FORM PTO-1390 (REV 5-93) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U S APPLICATION NO (If known, see 37 C.F R 1 5)
1241.18	09/806232

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP99/05349	29 September 1999	29 September 1998

TITLE OF INVENTION

DNAS ENCODING NOVEL POLYPEPTIDES

JC07 Rec'd PCT/PTO 28 MAR 2001

APPLICANT(S) FOR DO/EO/US

Motoharu Seiki

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the application time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information: Submission of Computer Readable Form; Form PCT/IPEA/409; Form PCT/IB/308; Copy of Published International Application No. WO00/18900; Form PCT/ISA/210.

U.S. APPLICATION NO. (If known, see 37 C F R 1 5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/806232	PCT/JP99/05349	1241.18

17. [X] The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5):		
Search Report has been prepared by the EP or JPO **$860.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.492(a)(1)) **$690.00**		
No international preliminary examination fee paid to USPTO (37 CFR 1.492 (a)(1)) but international search fee paid to USPTO (37 CFR 1.492(a)(2)) **$710.00**		
Neither international preliminary examination fee (37 CFR 1.492(a)(1)) nor international search fee (37 CFR 1.492(a)(2)) paid to USPTO **$1,000.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.492 (a)(4)) and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed	Number Extra	Rate		
Total Claims	114 - 20 =	94	X **$18.00**	$1692.00	
Independent Claims	6 - 3 =	3	X **$80.00**	$240.00	
Multiple dependent claim(s) (if applicable)			+ **$270.00**	$270.00	
			TOTAL OF ABOVE CALCULATIONS =	$3062.00	
[X] Applicant claims small entity status. See 37 C.F.R. 1.27. The fees indicated above are reduced by ½.				$1531.00	
			SUBTOTAL =	$1531.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
			TOTAL NATIONAL FEE =	$1531.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
			TOTAL FEES ENCLOSED =	$1531.00	
			Amount to be:		
			refunded	$	
			charged	$	

a. [X] A check in the amount of $ 1531.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1205. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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FITZPATRICK, CELLA, HARPER & SCINTO
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New York, NY 10112
Tel: (212) 218-2100
Fax: (212) 218-2200

SIGNATURE

Lawrence S. Perry
NAME

31,865
REGISTRATION NUMBER

NY_MAIN 156469 v 1

1241.18

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	:	Examiner: Not Yet Assigned
Motoharu Seiki	)	
	:	Group Art Unit: N/Y/A
Application No.: N/Y/A	)	
	:	
Filed: Currently herewith	)	
	:	
For: DNAS ENCODING NOVEL POLYPEPTIDES	)	
	:	March 27, 2001

Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to action on the merits, please amend the above-identified application as follows:

IN THE CLAIMS:

Please amend Claims 13, 18-21, 25, 26, 29, 30 and 32. A marked up copy of Claims 13, 18-21, 25, 26, 29, 30 and 32, showing the changes made thereto, is attached.

13. (Amended) A recombinant DNA that is obtained by integrating the DNA of any one of claims 11 or 12 into a vector.

18. (Amended) An oligonucleotide selected from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 9; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

19. (Amended) An oligonucleotide selected form an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 10; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

20. (Amended) A method of detecting an mRNA encoding the polypeptide of any one of claims 1 to 8 using an oligonucleotide selected from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 9; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

21. (Amended) A method of inhibiting expression of the polypeptide of any one of claims 1 to 8 using an oligonucleotide selected from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 9; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

25. (Amended) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said agent comprises the DNA of claim 9.

26. (Amended) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ

transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said agent comprises the DNA of claim 10.

29. (Amended) A vector for gene therapy for treating arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said vector is obtained by integrating the oligonucleotide of claim 18 into a vector.

30. (Amended) A vector for gene therapy for treating arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury,

inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said vector is obtained by integrating the oligonucleotide of claim 19 into a vector.

32. (Amended) The method of claim 31, wherein said compound that regulates the expression of a gene is detected by determining the amount of mRNA encoding the polypeptide.

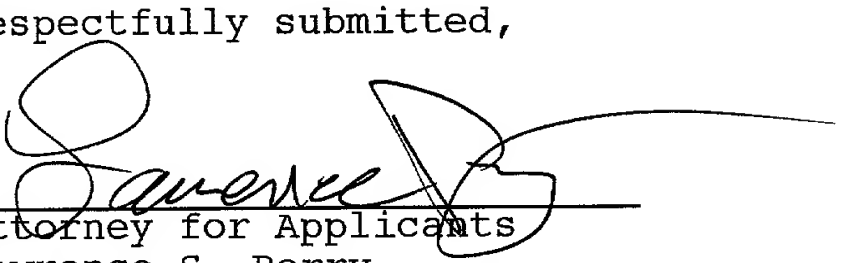
REMARKS

Claims 13, 18-21, 25, 26, 29, 30 and 32 have been amended to correct their dependency and conformity with accepted U.S. practice. No new matter has been added.

Entry hereof is earnestly solicited.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,



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NY_MAIN 156479 V1

VERSION WITH MARKINGS SHOWING CHANGES MADE TO CLAIMS

13. (Amended) A recombinant DNA that is obtained by integrating the DNA of any one of claims [9 to]11 or 12 into a vector.

18. (Amended) An oligonucleotide selected [form] from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 9 [or 11]; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

19. (Amended) An oligonucleotide selected form an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 10 [or 12]; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

20. (Amended) A method of detecting an mRNA encoding the polypeptide of any one of claims 1 to 8 using [the] an oligonucleotide [of claim 18 or 19] selected from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 9; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

21. (Amended) A method of inhibiting expression of the polypeptide of any one of claims 1 to 8 using [the] an oligonucleotide [of claim 18 or 19] selected from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 9; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

25. (Amended) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis,

arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said agent comprises the DNA of claim 9 [or 11].

26. (Amended) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said agent comprises the DNA of claim 10 [or 12].

29. (Amended) A vector for gene therapy for treating arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes,

wherein said vector is obtained by integrating the [DNA of claim 9 or 11, or the] oligonucleotide of claim 18 into a vector.

30. (Amended) A vector for gene therapy for treating arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said vector is obtained by integrating the [DNA of claim 10 or 12, or the] oligonucleotide of claim 19 into a vector.

32. (Amended) The method of claim 31, wherein said compound that regulates the expression of a gene is detected by determining the amount of mRNA encoding the polypeptide [of any one of claims 1 to 8].

#2.

1241.18

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Examiner: Not Yet Assigned
Motoharu Seiki	Group Art Unit: N/Y/A
Application No.: 09/806,232	
Filed: March 28, 2001	
For: DNAS ENCODING NOVEL POLYPEPTIDES	May 10, 2001

Commissioner for Patents
Washington, D.C. 20231

SUPPLEMENTAL PRELIMINARY AMENDMENT

Sir:

Further to the Preliminary Amendment filed March 28, 2001 and prior to action on the merits, please amend the above-identified application as follows:

IN THE SPECIFICATION

Please substitute the paragraph starting at page 39, line 5 and ending at line 8 with the following replacement paragraph. A marked-up copy of this paragraph, showing the changes made thereto, is attached.

In human, the expression of MT5-MMP was strong in the brain, and its expression was observed in the kidney and pancreas. The results of examination of its site-specific

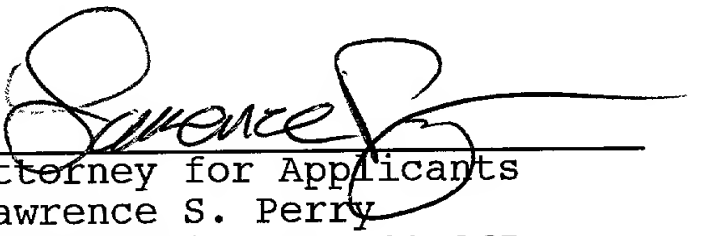
expression in the human brain revealed a characteristic expression in the cerebellum. High expression in the cerebellum was also confirmed in mouse.

REMARKS

The specification has been amended to correct an inadvertent word processing error. Since no new matter has been added, entry hereof is earnestly solicited.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,



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NY_MAIN 168275 v1

VERSION WITH MARKINGS TO SHOW CHANGES MADE TO SPECIFICATION

The paragraph starting at page 39, line 5 and ending at line 8 has been amended as follows.

In human, the expression of MT5-MMP [also] was strong in the brain, and its expression was observed in the kidney and pancreas. The results of examination of its site-specific expression in the human brain revealed a characteristic expression in the cerebellum. High expression in the cerebellum was also confirmed in mouse.

NY_MAIN 168275 v 1

1241.18

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	:	Examiner: Not Yet Assigned
Motoharu Seiki	)	
	:	Group Art Unit: N/Y/A
Application No.: N/Y/A	)	
	:	
Filed: Currently herewith	)	
	:	
For: DNAS ENCODING NOVEL POLYPEPTIDES	)	
	:	March 27, 2001

Commissioner for Patents
Washington, D.C. 20231

SUBMISSION OF COMPUTER READABLE FORM
UNDER 37 C.F.R. § 1.821(e)

Sir:

Applicants submit herewith a computer readable form under 37 C.F.R. § 1.821(e). The content of the computer readable form and the Sequence Listing filed herewith are the same.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

Respectfully submitted,

Attorney for Applicant
Lawrence S. Perry
Registration No. 31,865

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DESCRIPTION

DNAS ENCODING NOVEL POLYPEPTIDES

TECHNICAL FIELD

The present invention relates to novel membrane-type matrix metalloproteinase polypeptides; DNAs encoding the polypeptides; vectors comprising the DNAs; transformants transformed with the vectors; and a method of producing the polypeptides. Furthermore, the present invention relates to a method of searching for inhibitors or activators of the polypeptides using the polypeptides, a part thereof, or microorganisms or animal cells expressing the polypeptides or a part thereof, as well as a method of searching for compounds that regulate the gene expression of the polypeptides.

BACKGROUND ART

A group of enzymes generically termed "matrix metalloproteinases" (hereinafter, abbreviated to MMPs) that have metal ions at the active center are involved in the degradation of extracellular matrix composed of complicated components such as collagens, fibronectin, laminin and proteoglycans.

To date, the following MMPs have been reported: interstitial collagenase (MMP-1), gelatinase A (MMP-2), gelatinase B (MMP-9), stromelysin 1 (MMP-3), matrilysin (MMP-7), neutrophil collagenase (MMP-8), stromelysin 2 (MMP-10), stromelysin 3 (MMP-11), metallo-elastase (MMP-12), collagenase 3 (MMP-13), membrane type 1 MMP (MT1-MMP or MMP-14), membrane type 2 MMP (MT2-MMP or MMP-15), membrane type 3 MMP (MT3-MMP or MMP-16), membrane type 4 MMP (MT4-MMP or MMP-17), etc. (Protein, Nucleic Acid and Enzyme, 42, 2386 (1997)). These MMPs form a family, and each MMP is basically composed of an N-terminal propeptide domain, an active domain to which zinc ions bind, and a hemopexin-like domain. In MMP-7, no hemopexin-like domain is found. Transmembrane-type MMPs have a transmembrane domain and a intracellular domain at the C-terminal of the hemopexin-like domain.

A human MT4-MMP gene has already been reported [Puente, Cancer Research, 56, 944 (1996)]. However, a translation initiation site is not included in the nucleotide sequence of this gene, and this gene was defined as a human MT4-MMP gene simply because it comprises a nucleotide sequence containing MMP-like domains. Thus, it is difficult to consider that this gene encodes the full-length of MT4-MMP.

On the other hand, it is known that production of MT1-MMP is enhanced in patients with arthrosis deformans [Am. J. Pathol., 151, 245 (1997)]; that MMPs are important for the infiltration of leukocytes into tissues that is important in immunological and inflammatory reactions [J. Immunol., 156, 1 (1996)]; that MMP inhibitors prevent hepatitis [Eur. J. Pharmacol., 341, 105 (1998)]; and that MMP inhibitors are effective for treating corneal ulcer [Japanese Journal of Ophthalmology, 102, 270 (1998)].

It is also known that MMPs are important for cancer proliferation, infiltration and metastasis [Protein, Nucleic Acid and Enzyme, 42, 2386 (1997)], and it is reported that MMP inhibitors have carcinostatic activity [SCRIP, 2349, 20 (1998)].

Furthermore, it is suggested that MT4-MMP is expressed in leukocytes and thus may be involved in the migration and infiltration of leukocytes.

From what have been described so far, MMPs may be used for markers for diagnosing arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, and inhibitors of MMPs are useful for preventing or treating these diseases.

The already reported MT4-MMP gene [Cancer Research, 56, 944 (1996)] does not include a transcription initiation site nor has such a domain structure as seen in known membrane-type MMPs such as MT1-MMP. Therefore, this gene represents a sequence encoding a non-physiological peptide not expressed *in vivo*.

The present invention provides a novel, membrane-type matrix metalloproteinase polypeptide [hereinafter, sometimes abbreviated to MT4-MMP(2)] that is, different from the

hitherto reported MT4-MMP, physiologically active; a DNA encoding the metalloproteinase polypeptide; a method of producing the metalloproteinase polypeptide; and a method of screening for inhibitors or activators of the metalloproteinase polypeptide using the polypeptide or the DNA encoding the polypeptide.

The present invention also provides physiologically active, novel, human and mouse membrane-type matrix metalloproteinase polypeptides (hereinafter, abbreviated to human or mouse MT5-MMP); DNAs encoding the metalloproteinase polypeptides; a method of producing the metalloproteinase polypeptides; and a method of screening for inhibitors or activators of the metalloproteinase polypeptides using the polypeptides or the DNAs encoding the polypeptides.

DISCLOSURE OF THE INVENTION

The present inventor has made intensive and extensive researches based on the assumption that the known human MT4-MMP is not a protein having the inherent activity of MT4-MMP and that a true MT4-MMP protein having the activity should exist. Thus, the present invention has been achieved.

Also, the present inventor has made intensive and extensive researches based on the assumption that useful and novel membrane-type MMPs should exist other than hitherto known membrane-type MMPs that are considered useful in pharmaceutical purposes. Thus, the present invention has been achieved.

The present invention relates to the following inventions (1) to (32).

(1) A polypeptide consisting of the amino acid sequence as shown in SEQ ID NO: 1.

(2) A polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence of the polypeptide of (1) above and having metalloproteinase activity.

(3) A polypeptide consisting of the amino acid sequence as shown in SEQ ID NO: 2.

(4) A polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence of the polypeptide of (3) above and having metalloproteinase activity.

The deletion, substitution or addition mentioned in (2) and (4) above can be made by site-specific mutagenesis that was a well-known technique prior to the filing of the present application. "One or several amino acids" means the number of amino acids that can be deleted, substituted or added by site-specific mutagenesis. The polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence and having metalloproteinase activity can be prepared based on those methods described in Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press (1989) (hereinafter, abbreviated to Molecular Cloning 2nd Ed.); Current Protocols in Molecular Biology, Supplement 1-38, John Wiley & Sons (1987-1997) (hereinafter, abbreviated to Current Protocols 1-38); Nucleic Acid Research, 10, 6487 (1982); Proc. Natl. Acad. Sci. USA, 79, 6409 (1982); Gene, 34, 315 (1985), Nucleic Acids Research, 13, 4431 (1985); Proc. Natl. Acad. Sci. USA, 82, 488 (1985); Proc. Natl. Acad. Sci. USA, 81, 5662 (1984); Science, 224, 1431 (1984); PCT WO85/00817 (1985); Nature, 316, 601 (1985) and so forth.

(5) A polypeptide consisting of the amino acid sequence as shown in SEQ ID NO: 5.

(6) A polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence of the polypeptide of (5) above and having metalloproteinase activity.

(7) A polypeptide consisting of the amino acid sequence as shown in SEQ ID NO: 6.

(8) A polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence of the polypeptide of (7) above and having metalloproteinase activity.

(9) A DNA encoding the polypeptide of any one of (1) to (4) above.

(10) A DNA encoding the polypeptide of any one of (5) to (8) above.

(11) A DNA consisting of the nucleotide sequence of positions 86-1846 of SEQ ID NO: 3 or positions 100-1917 of SEQ ID NO: 4, or a DNA which hybridizes to the DNA under stringent conditions and which encodes a polypeptide having metalloproteinase activity.

The above expression "a DNA which hybridizes under stringent conditions" means a DNA that is obtained by colony hybridization, plaque hybridization, Southern blot

hybridization or the like using, as a probe, a DNA consisting of the nucleotide sequence of positions 86-1846 of SEQ ID NO: 3 or positions 100-1917 of SEQ ID NO: 4. Specifically, a DNA which can be identified by carrying out a hybridization at 65℃ in the presence of 0.7-1.0 mol/L NaCl using a filter on which the DNA derived from colony or plaque is immobilized, and then washing the filter in 0.1-2 x SSC (saline-sodium citrate) solution (1x SSC solution is composed of 150 mmol/L sodium chloride and 15 mmol/L sodium citrate) at 65℃.

Hybridization may be carried out based on those methods described in laboratory manuals such as Molecular Cloning 2nd Ed., Current Protocol in Molecular Biology, and DNA Cloning 1: Core Techniques, A Practical Approach, Second Edition, Oxford University Press (1995).

Specific examples of hybridizable DNAs include DNAs having at least 80% or more, preferably 95% or more homology to the nucleotide sequence of positions 86-1846 of SEQ ID NO: 3 or positions 100-1917 of SEQ ID NO: 4.

(12) A DNA consisting of the nucleotide sequence of positions 75-1928 of SEQ ID NO: 7 or positions 1-1935 of SEQ ID NO: 8, or a DNA which hybridizes to the DNA under stringent conditions and which encodes a polypeptide having metalloproteinase activity.

The above expression "a DNA which hybridizes under stringent conditions" means a DNA that is obtained by colony hybridization, plaque hybridization, Southern blot hybridization or the like using, as a probe, a DNA consisting of the nucleotide sequence of positions 75-1928 of SEQ ID NO: 7 or positions 1-1935 of SEQ ID NO: 8. Specifically, a DNA which can be identified by carrying out a hybridization at 65℃ in the presence of 0.7-1.0 mol/L NaCl using a filter on which the DNA derived from colony or plaque is immobilized, and then washing the filter in 0.1-2 x SSC (saline-sodium citrate) solution (1x SSC solution is composed of 150 mmol/L sodium chloride and 15 mmol/L sodium citrate) at 65℃.

Specific examples of hybridizable DNAs include DNAs having at least 80% or more, preferably 95% or more homology to the nucleotide sequence of positions 75-1928 of SEQ ID NO: 7 or positions 1-1935 of SEQ ID NO: 8.

(13) A recombinant DNA that is obtained by integrating the DNA of any one of (9) to (12) above into a vector.

(14) A transformant comprising the recombinant DNA of (13) above.

(15) The transformant of (14) above, wherein said transformant is a microorganism belonging to the genus *Escherichia*.

(16) The transformant of (15) above, wherein said microorganism belonging to the genus *Escherichia* is *Escherichia coli*.

(17) A method of producing the polypeptide of any one of (1) to (8) above, comprising culturing a transformant comprising a recombinant DNA obtained by integrating a DNA encoding the polypeptide into a vector in a medium, allowing the polypeptide to be produced and accumulated in the culture, and recovering the polypeptide from the culture.

(18) An oligonucleotide selected from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of (9) or (11) above; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

(19) An oligonucleotide selected from an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of (10) or (12) above; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

(20) A method of detecting an mRNA encoding the polypeptide of any one of (1) to (8) above using the oligonucleotide of (18) or (19) above.

(21) A method of inhibiting expression of the polypeptide of any one of (1) to (8) using the oligonucleotide of (18) or (19) above.

(22) A method of screening for an inhibitor or an activator of the polypeptide of any one of (1) to (8) above, which comprises using the polypeptide and a cell that expresses the polypeptide.

(23) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans,

rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said agent comprises the polypeptide of any one of (1) to (4) above.

(24) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said agent comprises the polypeptide of any one of (5) to (8) above.

(25) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said agent comprises the DNA of (9) or (11) above.

(26) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said agent comprises the DNA of (10) or (12) above.

(27) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact

dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said agent comprises the oligonucleotide of (18) above.

(28) A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said agent comprises the oligonucleotide of (19) above.

(29) A vector for gene therapy for treating arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said vector is obtained by integrating the DNA of (9) or (11) above, or the oligonucleotide of (18) above into a vector.

(30) A vector for gene therapy for treating arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said vector is obtained by integrating the DNA of (10) or (12) above, or the oligonucleotide of (19) above into a vector.

(31) A method of screening for a compound that regulates the expression of a gene encoding the polypeptide of any one of (1) to (8) above, which comprises contacting a cell that expresses the polypeptide with a test sample.

(32) The method of (31) above, wherein said compound that regulates the expression of a gene is detected by determining the amount of mRNA encoding the polypeptide of any one of (1) to (8) above.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows an alignment of the amino acid sequences of human MT5-MMP and mouse MT5-MMP with the amino acid sequences of human MT1-MMP, MT2-MMP, MT3-MMP and MT4-MMP(2).

Mark "*" indicates identical amino acid residues.

Mark "." indicates similar amino acid residues.

(Amino acid residues are represented by one-letter abbreviations.)

In this Figure, "kb" means kilobase pairs.

Fig. 2 shows the results of an experiment in which a mouse MT5-MMP partial peptide (i.e., propeptide domain + active domain; "MT5△C" in this Figure) of various concentrations was reacted with pro-MMP-2 to thereby examine the peptide's ability to cleave and activate pro-MMP-2.

As a positive control, APMA was used. As a result, activation was recognized in an MMP concentration dependent manner. In this Figure, "Active" shows activated MMP-2.

BEST MODES FOR CARRYING OUT THE INVENTION

Hereinbelow, the present invention will be described in detail.

[1] Acquisition of the DNAs encoding the Novel Matrix Metalloproteinase Polypeptides of the Present Invention

(1) Preparation of cDNA Libraries

In order to construct a cDNA library, total RNA or mRNA is prepared from an appropriate cell or tissue.

As a method for preparing total RNA, the guanidine thiocyanate-cesium trifluoroacetate method [Methods in Enzymology, 154, 3 (1987)], the acid guanidine thiocyanate/phenol/chloroform (AGPC) method [Analytical Biochemistry, 162, 156 (1987);

Experimental Medicine, 9, 1937 (1991)]; or the like may be used.

As a method for preparing mRNA (as poly(A)$^+$ RNA) from total RNA, a method using oligo(dT) immobilized cellulose column (Molecular Cloning 2nd Ed.), a method using oligo(dT) latex [Cell Engineering, Supplement 8, "New Cell Engineering Experiment Protocols", SHUJUNSHA Co., pp.48-52; Nucleic Acids Res., Symposium Series, 19, 61 (1988)] or the like may be used.

Alternatively, mRNA may be prepared directly from a tissue or cell using a commercial kit such as First Track mRNA Isolation Kit (Invitrogen) or Quick Prep mRNA Purification Kit (Pharmacia).

In the case of MT4-MMP(2), preferably, types of cDNA libraries which contained ESTs of the DNA encoding MT4-MMP found in databases are ascertained, and then cells or tissues that were used for the construction of those libraries, or cell strains or the like derived from those tissues may be used as an appropriate cell or tissue. In the case of MT5-MMP, it is preferable to use tissues such as brain and kidney or cell strains derived from those tissues as an appropriate cell or tissue.

From the resultant total RNA or mRNA, a cDNA library is constructed by conventional methods.

Specific examples of methods for constructing cDNA libraries include those described in Molecular Cloning 2nd Ed.; Current Protocols 1-38; DNA Cloning 1: Core Techniques, A practical Approach, Second Edition, Oxford University Press (1995); etc. or methods using commercial kits such as SuperScript Plasmid System for cDNA Synthesis and Plasmid Cloning manufactured by Gibco BRL and ZAP-cDNA Synthesis Kit manufactured by Stratagene.

As a cloning vector for constructing a cDNA library, any vector, such as a phage vector or plasmid vector, may be used as long as it is capable of autonomous replication in *E. coli* K12 strain.

Specifically, ZAP Express [Stratagene; Strategies, 5, 58 (1992)], pBluescript II SK(+) [Nucleic Acids Research, 17, 9494 (1989)], Lamda ZAP II {Stratagene), λgt10, λgt11 [DNA Cloning, A Practical Approach, 1, 49 (1985)], λ TriplEx (Clontech), λ ExCell

(Pharmacia), pT7T318U (Pharmacia), pcD2 [Mol. Cell. Biol., 3, 280 (1983)], pUC18 [Gene, 33, 103 (1985)], pAMo [J. Biol. Chem., 268, 22782-22787 (1993); also called as "pAMoPRC3Sc" (Japanese Unexamined Patent Publication No. 05-336963) or the like may be used.

As a host microorganism, any microorganism may be used as long as it belongs to *Escherichia coli*. Specifically, *Escherichia coli* XL1-Blue MRF' [Stratagene; Strategies 5, 81 (1992)], *Escherichia coli* C600 [Genetics, 39, 440 (1954)], *Escherichia coli* Y1088 [Science, 222, 778 (1983)], *Escherichia coli* Y1090 [Science, 222, 778 (1983)], *Escherichia coli* NM522 [J. Mol. Biol., 166, 1 (1983)], *Escherichia coli* K802 [J. Mol. Biol., 16, 118 (1966)], *Escherichia coli* JM105 [Gene, 38, 275 (1985)], *Escherichia coli* SOLRTM Strain (Stratagene), *Escherichia coli* LE392 (Molecular Cloning 2nd Ed.) or the like may be used.

In addition to cDNA libraries constructed by the above-described methods, commercial cDNA libraries may also be used.

Examples of commercial cDNA libraries include cDNA libraries of individual organs derived from animals such as human, bovine, mouse, rat or rabbit manufactured by Clontech, Lifetech Oriental, etc.

(2) Aquisition of the DNAs of the Invention

cDNA clones containing the DNA of the present invention may be selected from the cDNA library prepared in (1) above by such method as colony hybridization or plaque hybridization (Molecular Cloning 2nd Ed.) using a radioactively or fluorescently labeled probe.

As a probe for MT4-MMP(2) gene, an oligonucleotide based on the nucleotide sequence of a DNA encoding MT4-MMP (a part of which has been elucidated) may be used. For MT5-MMP gene, an oligonucleotide based on the nucleotide sequence of a DNA encoding MT3-MMP may be used.

From the resultant clones of interest, mRNA is obtained as described above and then cDNA is synthesized.

An adaptor is added to both ends of the resultant cDNA. Using a primer based on the

sequence of this adaptor and a gene-specific primer based on the partially known sequence of the gene of interest, 5' RACE (rapid amplification of cDNA ends) and 3' RACE [Proc. Natl. Acad. Sci. USA, 85, 8998 (1988)] are carried out to obtain a cDNA fragment located 5' to the primer sequence and a cDNA fragment located 3' to the primer sequence.

By ligating the resultant cDNA fragments, a full-length cDNA can be obtained.

The nucleotide sequence of the thus obtained DNA fragment can be determined by integrating into a vector the fragment as it is or the fragment digested with an appropriate restriction enzyme by conventional methods and then analyzing the sequence by conventional methods such as the dideoxy method by Sanger et al. [Proc. Natl. Acad. Sci. USA, 74, 5463 (1977)] or with a DNA sequencer manufactured by Perkin Elmer (373A DNA Sequencer), Pharmacia, LI-COR, etc.

In order to determine the nucleotide sequence of the genomic DNA fragment encoding the polypeptide of the present invention, conventional methods for chromosomal DNA cloning (Molecular Cloning 2nd Ed.) can be used.

Briefly, chromosomal DNA from cells expressing the polypeptide of the present invention [such as monocytic THP-1 cells for MT4-MMP(2); such as brain or kidney cells for MT5-MMP] is digested with a restriction enzyme. The digested fragments are cloned into a conventional plasmid vector or phage vector to construct a genomic library.

The genomic library is screened using, as a probe, the DNA fragment obtained and sequenced as described above in the same manner as in the cDNA cloning described above. Thus, clones containing the genomic gene encoding the polypeptide of the present invention can be obtained.

Using the resultant clones, the nucleotide sequence of the genomic gene can be determined by the above-described method.

It is also possible to obtain a DNA of interest derived from other tissues or other animals (e.g. human) by selecting DNAs that hybridize to the DNA obtained by the above-described method under stringent conditions.

Alternatively, a DNA of interest may be chemically synthesized with a DNA synthesizer based on the nucleotide sequence information obtained by the above-described

method. As a DNA synthesizer, one using the thiophosphite method manufactured by Shimadzu Corp., a DNA synthesizer model 392 using the phosphoamidite method manufactured by Perkin Elmer, or the like may be enumerated.

The novelty of the nucleotide sequence obtained can be confirmed by searching DNA sequence databases of GenBank, EMBL, DDBJ, etc. using a homology search program such as BLAST. If the nucleotide sequence is found to be novel, it is converted into an amino acid sequence. Then, amino acid sequence databases of GenPept, PIR, Swiss-Prot, etc. are searched using a homology search program such as FASTA or FrameSearch to thereby search for existing genes having homology to the novel nucleotide sequence.

As a DNA encoding MT4-MMP(2), the polypeptide of the present invention, that has been confirmed to have a novel nucleotide sequence by the above-described method, a DNA having the nucleotide sequence as shown in SEQ ID NO: 3 or SEQ ID NO: 4 may be given, for example.

As a plasmid comprising a DNA having the nucleotide sequence as shown in SEQ ID NO: 3, plasmid pmMT4/pBSSK may be given. As a plasmid comprising a DNA having the nucleotide sequence as shown in SEQ ID NO: 4, plasmid phMT4/pBSIIKS may be given.

Escherichia coli pmMT4/pBSSK comprising plasmid pmMT4/pBSSK and *Escherichia coli* phMT4/pBSIIKS comprising plasmid phMT4/pBSIIKS were deposited as FERM BP-6528 and FERM BP-6530, respectively, on September 25, 1998 with National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology located at 1-3, Higashi 1-chome, Tsukuba City, Ibaraki Pref., Japan (postal code: 305-8566).

As a DNA encoding MT5-MMP, another polypeptide of the present invention, that has been confirmed to have a novel nucleotide sequence by the above-described method, a DNA having the nucleotide sequence as shown in SEQ ID NO: 7 or SEQ ID NO: 8 may be given, for example.

As a plasmid comprising a DNA having the nucleotide sequence as shown in SEQ ID NO: 7, plasmid pmMT5/pBSSK may be given. As a plasmid comprising a DNA having the nucleotide sequence as shown in SEQ ID NO: 8, plasmid phMT5/pGEM may be given.

Escherichia coli pmMT5/pBSSK comprising plasmid pmMT5/pBSSK and

Escherichia coli phMT5/pGEM comprising plasmid phMT5/pGEM were deposited as FERM BP-6529 and FERM BP-6531, respectively, on September 25, 1998 with National Institute of Bioscience and Human-Technology, Agency of Industrial Science and Technology located at 1-3, Higashi 1-chome, Tsukuba City, Ibaraki Pref., Japan (postal code: 305-8566).

(3) Preparation of the Oligonucleotides of the Invention

Using the DNAs and DNA fragments of the present invention obtained in the above-described method, oligonucleotides (anti-sense and sense) comprising a partial sequence of the DNAs of the present invention can be prepared by conventional methods or with the DNA synthesizer mentioned above.

Examples of such oligonucleotides include a DNA having the same sequence as that of consecutive 5 to 60 bases within the nucleotide sequences of the above-described DNAs, or a DNA complementary thereto. Specifically, as oligonucleotides comprising a partial sequence of MT4-MMP(2) gene, a DNA having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases in the nucleotide sequence as shown in SEQ ID NO: 3 or 4, or a DNA complementary thereto may be given. As oligonucleotides comprising a partial sequence of MT5-MMP gene, a DNA having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases in the nucleotide sequence as shown in SEQ ID NO: 7 or 8, or a DNA complementary thereto may be given. When oligonucleotides are used as a sense primer and an anti-sense primer, the above-described oligonucleotides are preferably used which are not greatly different between the selected two in melting temperature (Tm) and in the number of bases.

Furthermore, derivatives of these oligonucleotides may also be used as the oligonucleotide of the present invention.

Some of the examples of such oligonucleotide derivatives include oligonucleotide derivatives in which phosphodiester bonds are converted to phosphorothioate bonds; oligonucleotide derivatives in which phosphodiester bonds are converted to N 3'-P5' phosphoamidate bonds; oligonucleotide derivatives in which ribose and phosphodiester bonds are converted to peptide-nucleic acid bonds; oligonucleotide derivatives in which uracil is

substituted by C-5 propynyluracil; oligonucleotide derivatives in which uracil is substituted by C-5 thiazoluracil; oligonucleotide derivatives in which cytosine is substituted by C-5 propynylcytosine; oligonucleotide derivatives in which cytosine is substituted by phenoxazine-modified cytosine; oligonucleotide derivatives in which ribose is substituted by 2'-O-propylribose; or oligonucleotide derivatives in which ribose is substituted by 2'-methoxyethoxyribose [Cell Engineering, 16, 1463 (1997)].

[2] Preparation of the Matrix Metalloproteinase Polypeptides of the Invention

(1) Preparation of Transformants

In order to express in a host cell the DNA of the present invention obtained by the method described in [1] above, methods described in Molecular Cloning 2nd Ed. and Current Protocols 1-38, for example, may be used.

Briefly, a recombinant expression vector is prepared by inserting the DNA of the present invention downstream of a promoter in an appropriate vector. Then, by introducing the recombinant vector into a host cell, a transformant that expresses the polypeptide of the present invention can be obtained.

As a host cell, any cell such as a bacterium, yeast, animal cell, or insect cell may be used as long as it is capable of expressing the gene of interest.

As an expression vector, a vector which is capable of autonomously replicating or integrating into chromosome in the above host cell, and which comprises a promoter at a site appropriate for transcription of the DNA of the present invention, is used.

When a procaryote such as a bacterium is used as the host cell, it is preferred that the expression vector for the polypeptide gene of the present invention be capable of autonomous replication in the procaryote and, at the same time, a recombinant vector composed of a promoter, a ribosome binding sequence, the DNA of the present invention, and a transcription termination sequence. The vector may also contain a gene that controls the promoter.

Examples of expression vectors which may be used in the present invention include pKK233-2 (Pharmacia), pSE280 (Invitrogen), pGEMEX-1 (Promega), pQE-8 (Qiagen), pKYP10 (Japanese Unexamined Patent Publication No. 58-110600), pKYP200 [Agric. Biol.

Chem., 48, 669 (1984)], pLSA1 [Agric. Biol. Chem., 53, 277 (1989)], pGEL1 [Proc. Natl. Acad. Sci. USA, 82, 4306 (1985)], pBluescript II SK(-) (Stratagene), pGEX (Pharmacia), and pET-3 (Novagen).

As a promoter, any promoter may be used as long as it can direct the expression of the gene of interest in a host cell such as *E. coli* or *Bacillus subtilis*. For example, an *E. coli*- or phage-derived promoter such as trp promoter (Ptrp), lac promoter, PL promoter, PR promoter or T7 promoter; SP01 promoter; SP02 promoter; or penP promoter may be used. An artificially designed and altered promoter such as a promoter in which two Prtp promoters are connected in series (Ptrp x 2), tac promoter, lacT7 promoter, or let 1 promoter may also be used.

As a ribosome binding sequence, it is preferable to use a plasmid in which the distance between Shine-Dalgarno sequence and the initiation codon is appropriately adjusted (e.g., 6-18 bp).

In the recombinant vector of the present invention, it is not necessarily required for the expression of the DNA of the present invention to contain a transcription termination sequence, but it is desirable to locate such a sequence immediately downstream of the structural gene.

As a host cell, a microorganism belonging to the genus *Escherichia, Serratia, Bacillus, Brevibacterium, Corynebacterium, Microbacterium, Pseudomonas* or the like may be used. Specific examples of host cells which may be used in the present invention include *Escherichia coli* XL1-Blue, *Escherichia coli* XL2-Blue, *Escherichia coli* DH1, *Escherichia coli* MC1000, *Escherichia coli* KY3276, *Escherichia coli* W1485, *Escherichia coli* JM109, *Escherichia coli* HB101, *Escherichia coli* No.49, *Escherichia coli* W3110, *Escherichia coli* NY49, *Serratia ficaria, Serratia fonticola, Serratia liquefaciens, Serratia marcescens, Bacillus subtilis, Bacillus amyloliquefaciens, Brevibacterium ammmoniagenes, Brevibacterium immariophilum* ATCC14068, *Brevibacterium saccharolyticum* ATCC14066, *Corynebacterium glutamicum* ATCC13032, *Corynebacterium glutamicum* ATCC14067, *Corynebacterium glutamicum* ATCC13869, *Corynebacterium acetoacidophilum* ATCC13870, *Microbacterium ammoniaphilum* ATCC15354, and *Pseudomonas* sp. D-0110.

As a method for introducing the recombinant vector, any method of introducing

DNA into the above host cell may be used. For example, the method using calcium ions [Proc. Natl. Acad. Sci., USA, 69, 2110 (1972)], the protoplast method (Japanese Unexamined Patent Publication No. 63-248394), or electroporation [Gene, 17, 107 (1982); Molecular & General Genetics, 168, 111 (1979)] may be used.

When a yeast strain is used as the host cell, an expression vector such as YEp13 (ATCC37115), YEp24 (ATCC37051), YCp50 (ATCC37419), pHS19, or pHS15 may be used.

As a promoter, any promoter that can direct the expression of the gene of interest in yeast may be used. For example, PH05 promoter, PGK promoter, GAP promoter, ADH promoter, gal 1 promoter, gal 10 promoter, heat shock polypeptide promoter, MF α 1 promoter, or CUP 1 promoter may be used.

As a host cell, a yeast strain belonging to the genus *Saccharomyces, Schizosaccharomyces, Kluyveromyces, Trichosporon, Schwanniomyces, Pichia* or the like may be used. Specific examples of yest strains that may be used in the present invention include *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces lactis, Trichosporon pullulans, Schwanniomyces alluvius*, and *Pichia pastoris*.

As a method for introducing the recombinant vector, any method of introducing DNA into yeast may be used. For example, electroporation [Methods in Enzymology, 194, 182 (1990)], the spheroplast method [Proc. Natl. Acad. Sci., USA, 81, 4889 (1984)], the lithium acetate method [Journal of Bacteriology, 153, 163 (1983)] or the like may be enumerated.

When an animal cell is used as the host, an expression vector such as pAGE107 (Japanese Unexamined Patent Publication No. 3-22979; Cytotechnology, 3, 133 (1990)], pAS3-3 (Japanese Unexamined Patent Publication No. 2-227075), pCDM8 [Nature, 329, 840 (1987)], pcDNAI/Amp (Invitrogen), pREP4 (Invitrogen), or pAGE103 [Journal of Biochemistry, 101, 1307 (1987)] may be used.

As a promoter, any promoter that can direct the expression of the gene of interest in animal cells may be used. Examples of promoters that may be used in the present invention include the promoter of the IE (immediate early) gene of cytomegalovirus (CMV), the early promoter of SV40, a metallothionein promoter, a retrovirus promoter, a heat shock

promoter and SR α promoter. Alternatively, the enhancer of the IE gene of human CMV may be used in combination with the promoter thereof.

Examples of animal cells that may be used in the present invention include human cells such as Namalwa cells, HEK293 cells (ATCC: CRL-1573); simian cells such as COS cells; and Chinese hamster cells such as CHO cells, HBT5637 (Japanese Unexamined Patent Publication No. 63-299).

As a method for introducing the recombinant vector, any method of introducing DNA into animal cells may be used. For example, electroporation [Cytotechnology, 3, 133 (1990)], the calcium phosphate method (Japanese Unexamined Patent Publication No. 2-227075), or lipofection [Proc. Natl. Acad. Sci. USA, 84, 7413 (1987); Virology, 52, 456 (1973)] may be used.

When an insect cell is used as the host, it is possible to express the polypeptide of the present invention according to methods described in, for example, Baculovirus Expression Vectors, A Laboratory Manual, W.H. Freeman and Company, New York (1992); Current Protocols 1-38; and Bio Technology, 6, 47 (1988).

Briefly, a recombinant gene transfer vector and Baculovirus are co-introduced into an insect cell to thereby obtain a recombinant virus in the supernatant of the insect cell culture. Then, the insect cell is infected with the recombinant virus further to allow the production of the polypeptide of the present invention.

As a gene transfer vector that may be used in the above method, pVL1392, pVL1393, pBlueBacIII (all of which are manufactured by Invitrogen) may be enumerated, for example.

As a Baculovirus that may be used in the above method, Autographa californica nuclear polyhedrosis virus that infects insects belonging to the subfamily Hadeniae may be given, for example.

As an insect cell that may be used in the above method, *Spodoptera frugiperda* ovary cells Sf9 and Sf21 [Baculovirus Expression Vectors, A Laboratory Manual (1992)]; a *Trichoplusia ni* ovary cell High5 (Invitrogen); or the like may be enumerated.

As a method of co-introducing a gene transfer vector and Baculovirus into an insect cell

for preparing a recombinant virus, the calcium phosphate method (Japanese Unexamined Patent Publication No. 2-227075) or lipofection [Proc. Natl. Acad. Sci. USA, 84, 7413 (1987)] may be enumerated, for example.

As a method of expressing the gene, in addition to direct expression, such as secretion production or fusion protein expression may be carried out based on the methods described in Molecular Cloning 2nd Ed.

When the polypeptide of the present invention is expressed by a yeast strain, animal cell or insect cell, a polypeptide to which sugars or sugar chains have been attached can be obtained.

The polypeptide of the present invention can be prepared by culturing the transformant obtained as described above in a medium, allowing the polypeptide of the present invention to be produced and accumulated in the culture, and recovering the polypeptide from the culture.

It is also possible to express the polypeptide of the present invention in a patient *in vivo* by introducing an appropriate expression vector that directs expression of the polypeptide of the present invention into cells taken from the patient's living body and then returning the cells into the body.

(2) Culturing of Transformants

The culturing of the transformant of the present invention in a medium is carried out by conventional methods used for culturing hosts.

As a medium to culture the transformant obtained from a procaryotic host such as *E. coli* or an eucaryotic host such as yeast, either a natural or synthetic medium may be used as long as it contains carbon sources, nitrogen sources and inorganic salts assimilable by the microorganism and is suitable for efficient culturing of the transformant.

As carbon sources, any carbon source may be used as long as it is assimilable by the microorganism. For example, carbohydrates such as glucose, fructose, sucrose, or molasses, starch or starch hydrolysate containing them; organic acids such as acetic acid, propionic acid; and alcohols such as ethanol and propanol may be used.

As nitrogen sources, ammonia; ammonium salts of inorganic or organic acids such as

ammonium chloride, ammonium sulfate, ammonium acetate, ammonium phosphate; other nitrogen-containing compounds; Peptone; meat extract; yeast extract; corn steep liquor; casein hydrolysate; soybean meal and soybean meal hydrolysate; various fermented microorganism cells and digested products thereof; and the like may be used.

As inorganic substances, potassium dihydrogen phosphate, dipotassium hydrogen phosphate, magnesium phosphate, magnesium sulfate, sodium chloride, iron(II) sulfate, manganese sulfate, copper sulfate, calcium carbonate and the like may be used.

Usually, culturing is carried out under aerobic conditions, by such as shaking culture or submerged aeration agitation culture. The culturing temperature is preferably between 15 to 40℃, and the culturing period is usually 16 to 96 hrs. During the culturing, the pH is maintained at 3.0 to 9.0. The pH adjustment is carried out using an inorganic or organic salt, an alkali solution, urea, calcium carbonate, ammonia or the like.

During the culturing, an antibiotic such as ampicillin or tetracycline may be added to the medium if necessary.

When a microorganism transformed with an expression vector using an inducible promoter is cultured, an inducer may be added to the medium if necessary. For example, when a microorganism transformed with an expression vector using Lac promoter is cultured, isopropyl-β-D-thiogalactopyranoside or the like may be added. When a microorganism transformed with an expression vector using trp promoter is cultured, indoleacrylic acid or the like may be added.

As a medium to culture a transformant obtained from an animal cell as a host, commonly used RPMI1640 medium [The Journal of the American Medical Association, 199, 519 (1967)], Eagle's MEM medium [Science, 122, 501 (1952)], DMEM medium [Virology, 8, 396 (1959)], 199 medium [Proceeding of the Society for the Biological Medicine, 73, 1 (1950)] or one of these media supplemented with fetal bovine serum, etc. may be used.

Usually, the culturing is carried out at pH 6-8, at 30-40℃ in the presence of 5% CO_2 for 1 to 7 days.

During the culturing, an antibiotic such as kanamycin, penicillin, or streptomycin may be added to the medium if necessary.

As a medium to culture a transformant obtained from an insect cell as a host, commonly used TNM-FH medium (Pharmingen), Sf-900 II SFM medium (Life Technologies), ExCell400 or ExCell405 (both from JRH Biosciences), Grace's Insect Medium [Nature, 195, 788 (1962)] or the like may be used.

Usually, culturing is carried out at pH 6-7 at 25-30℃ for 1 to 5 days.

During the culturing, an antibiotic such as gentamycin may be added to the medium if necessary.

(3) Isolation and Purification of the Expressed Polypeptides

Conventional methods of enzyme isolation/purification may be used to isolate and purify the polypeptides expressed by the method described above from the culture of the above-described transformant. For example, when the polypeptide of the present invention is expressed in a dissolved state in cells, the cells are harvested by centrifugation after completion of the culturing, and then suspended in an aqueous buffer. Subsequently, the cells are disrupted with a sonicator, French press, Manton-Gaulin homogenizer, Dynomill or the like to thereby obtain a cell-free extract, which is then centrifuged to obtain a supernatant. From this supernatant, a purified sample may be obtained by conventional enzyme isolation/purification methods. For example, the solvent extraction method; salting out with ammonium sulfate or the like; desalting; precipitation with organic solvents; anion exchange chromatography using resins such as Q-Sepharose, diethylaminoethyl (DEAE)-Sepharose, DIAION HPA-75 (Mitsubishi Chemical Corp.); cation exchange chromatography using resins such as S-Sepharose FF (Pharmacia); hydrophobic chromatography using resins such as butyl Sepharose, phenyl Sepharose; gel filtration using molecular sieve; affinity chromatography; and electrophoresis such as chromatofocusing, isoelectric focusing; may be used independently or in combination.

When the polypeptide of the present invention is expressed in an insoluble form within cells, the cells are harvested and disrupted in the same manner as described above. Then, the cells are centrifuged to obtain the precipitate fraction, from which the polypeptide is recovered by conventional methods. Subsequently, the polypeptide in an insoluble form is solubilized

with a protein-denaturing agent. The resultant solubilized solution is diluted until the solution no longer contains the denaturing agent or the concentration of the denaturing agent becomes so low that no protein denaturation would occur; or the solubilized solution is dialyzed. Thus, the normal steric structure of the polypeptide is restored. Subsequently, a purified sample can be obtained by using the isolation/purification methods described above.

When the polypeptide of the present invention or a derivative thereof (such as sugar-modified polypeptide) is secreted out of cells, the polypeptide or the derivative can be recovered from the culture supernatant. Briefly, the culture is treated by centrifugation, etc. in the same manner as described above to obtain the soluble fraction. From this soluble fraction, a purified sample can be obtained by using the isolation/purification methods described above. When the polypeptide of the present invention or a derivative thereof (such as sugar-modified polypeptide) is expressed on cell surfaces, the membrane fraction of the cultured cells is dissolved with a surfactant to obtain the soluble fraction. From this soluble fraction, a purified sample can be obtained by using the isolation/purification methods described above.

Alternatively, the polypeptide of the present invention may be prepared by chemical synthesis methods such as the Fmoc (fluorenylmethyloxycarbonyl) method and the tBoc (t-butyloxycarbonyl) method. The polypeptide of the present invention may also be chemically synthesized with peptide synthesizers manufactured by Advanced ChemTech, Perkin Elmer, Pharmacia, Protein Technology Instrument, Synthecell-Vega, PerSeptive, Shimadzu Corp. and so forth.

[3] Detection of the Biological Activity of the Polypeptides of the Invention

The proteinase activity of the polypeptides of the present invention obtained by the method described in [2] above is determined by subjecting a peptide or protein degraded by the polypeptides of the present invention electrophoresis or column chromatography. Alternatively, the activity is determined by measuring degradation of a fluorescence- or isotope-labeled peptide or protein by the polypeptide of the present invention. It is also possible to detect the activity by measuring the state of activation of an enzyme that is

activated by excision of a peptide. The activity may also be measured by using a gel containing a peptide that is degraded by the enzyme in the same manner as in gelatin zymography.

[4] Search for and Identification of Inhibitors or Activators of the Polypeptides of the Invention

A test sample is added to those cells expressing the polypeptide of the present invention prepared by the method described in [2] above, or the polypeptide of the present invention purified by the method described in [2] above from recombinant *E. coli* cells expressing the polypeptide of the present invention prepared by the method described in [2] above.

Then, by comparing the proteinase activity of the polypeptide of the present invention in the presence of the test sample with the activity in the absence of the test sample, it is possible to screen for a substance that enhances the proteinase activity (activator) or a substance that inhibits the proteinase activity (inhibitor).

Specific examples of test samples include synthetic compounds, naturally occurring proteins, artificially synthesized proteins, peptides, saccharides, lipids, modified products or derivatives of these substances; urine, body fluids, tissue extracts, cell culture supernatants and cell extracts from mammals (such as mouse, rat, guinea pig, hamster, pig, sheep, bovine, equine, canine, feline, simian, or human); non-peptidic compounds; fermentation products; and extracts from plants and other organisms.

When a peptide is used as a test sample, a random peptide library may be utilized. Examples of random peptide libraries that may be used in the present invention include peptides on phage [Proc. Natl. Acad. Sci. USA, 87, 6378 (1990); PCT Patent Application Number 96/40189] and peptides on plasmids [United States Patent No. 5,270,170; United States Patent No. 5,338,665].

Peptides that bind to MT4-MMP(2) of the present invention can be obtained by screening a random peptide library. Examples of random peptide libraries that may be used in the present invention include peptides on phage [Proc. Natl. Acad. Sci. USA, 87, 6378 (1990); PCT Patent Application Number 96/40189] and peptides on plasmids [United States

Patent No. 5,270,170; United States Patent No. 5,338,665].

[5] Uses of the DNAs and Polypeptides of the Invention

(1) The DNA of the present invention may be used as a probe in Northern hybridization on RNA that is extracted from human tissues or human-derived cells in the same manner as described in (2) of Section [1] above, to thereby detect or quantitatively determine the mRNA of the polypeptide gene of the present invention in the tissues or cells. By comparing the amounts of RNA expressed in various tissues, the tissue distribution of the polypeptide of the present invention can be elucidated.

Alternatively, the oligonucleotide of the present invention may be used as a primer specific to the DNA of the present invention in RT-PCR [reverse transcription PCR; PCR protocols (1990)] on RNA that is extracted from human tissues or human-derived cells in the same manner as described in (2) of Section [1] above, to thereby detect or quantitatively determine the mRNA of the polypeptide gene of the present invention. These methods of quantitative determination of the mRNA of the polypeptide gene may be used in the diagnosis of disease states in which the gene is involved.

By quantification of the mRNA encoding the polypeptide in various disease model animals, it is possible to reveal the importance of the gene product in diseases. Furthermore, it is possible to evaluate a drug by comparing the amount of expression of the mRNA encoding the polypeptide in the presence or absence of the drug.

(2) The DNA of the present invention or an oligonucleotide having a nucleotide sequence identical with or complementary to a partial nucleotide sequence of the DNA may be used as a probe to carry out *in situ* hybridization [Methods in Enzymology, 254, 419 (1995)] on human tissue section. As a result, more detailed information on the distribution of the polypeptide of the present invention can be obtained, e.g. cells expressing the polypeptide in a given tissue can be specified.

Information as to in which tissue or cell the polypeptide of the present invention is expressed, and information as to what stimulation given to cells changes the amount of expression of the polypeptide obtained by the above-described methods will be useful in

elucidating the physiological functions of the polypeptide of the present invention and its involvement in diseases.

(3) The DNA of the present invention may be used as a probe to carry out Southern hybridization (Molecular Cloning 2nd Ed.) on genomic DNA. As a result, mutations in the gene encoding the polypeptide of the present invention can be detected. By detecting such mutations, it is possible to diagnose those diseases which may be caused by mutations of the gene. Specifically, with respect to MT4-MMP(2), diseases such as arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, and inflammations associated with infiltration of leukocytes may be diagnosed. With respect to MT5-MMP, diseases such as arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease, brain tumor, and inflammations associated with infiltration of leukocytes may be diagnosed.

(4) The anti-sense oligonucleotides (RNA/DNA) of the present invention are expected to be applicable to treatment or prevention of diseases in which the gene encoding the polypeptide of the present invention may be involved in their onset, by inhibiting the transcription of the gene or the translation of the mRNA [Chemistry 46, 681 (1991); Bio Technology, 9, 358 (1992)]. With respect to MT4-MMP(2), specific examples of such diseases include arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, and inflammations associated with infiltration of leukocytes. With respect to MT5-MMP, specific examples of such diseases include arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor,

brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease, brain tumor, and inflammations associated with infiltration of leukocytes.

The above-described anti-sense oligonucleotide is designed and prepared based on a partial nucleotide sequence of the DNA encoding the polypeptide of the present invention, preferably a nucleotide sequence complementary to 10-50 bases within the translation initiation region, and then administered into the living bodies of subjects.

Pharmaceuticals containing the DNA of the present invention are prepared or administered in the same manner as described below except that the DNA of the present invention is used instead of the polypeptide of the present invention.

(5) The polypeptide of the present invention can be obtained by using the DNA of the present invention in accordance with the method described in [2] above. With respect to MT4-MMP(2), a polypeptide of the present invention is used for a diagnostic agent, therapeutic agent or prophylactic agent for diseases such as arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, and inflammations associated with infiltration of leukocytes. With respect to MT5-MMP, a polypeptide of the present invention is used for a diagnostic agent, therapeutic agent or prophylactic agent for diseases such as arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease, brain tumor, and inflammations associated with infiltration of leukocytes is contemplated.

Although it is possible to administer the polypeptide of the present invention alone as a diagnostic agent or therapeutic agent, usually it is preferred that the polypeptide of the present invention be administered as a pharmaceutical preparation obtained by mixing the polypeptide with one or more pharmacologically acceptable carriers and formulating by any of the well-known methods in the technical field of pharmaceutics. Preferably, a sterile solution of the

polypeptide dissolved in water or an aqueous carrier such as an aqueous solution of NaCl, glycine, glucose or human albumin is used. Pharmacologically acceptable additives such as buffers and isotonic agents that bring liquid preparations close to physiological conditions may also be added. For example, sodium acetate, sodium chloride, sodium lactate, potassium chloride, or sodium citrate may be added. The pharmaceutical preparation may be freeze-dried for storage and dissolved in an appropriate solvent at the time of use.

It is desirable to select the best route of administration that would be most effective for the treatment intended. Usually, parenteral routes such as subcutaneous, intramuscular, intravenous, or intratracheal route are used.

(6) The DNAs of the present invention (sense DNAs and anti-sense DNAs) or oligonucleotides comprising a part of the nucleotide sequences thereof may be incorporated as a single-stranded or double-stranded DNA or oligonucleotide into viral vectors such as retrovirus, adenovirus, adeno-associated virus or other vectors to prepare vectors for gene therapy, and may be used in such therapy.

EXAMPLES

Hereinbelow, the present invention will be described more specifically with reference to the following Examples. However, the scope of the present invention is not limited by these Examples.

EXAMPLE 1. Cloning of the Gene of Mouse MT4-MMP-Related Protein [MT4-MMP(2)]

Since MT4-MMP gene is highly expressed in the human brain, a brain cDNA library from mouse 17-day embryo was prepared using ZAP-cDNA Synthesis Kit (Stratagene) according to the manual attached to the Kit.

Using a partial sequence of the human MT4-MMP gene (positions 233-1899 of SEQ ID NO: 17) as a probe, the resultant cDNA library was screened by plaque hybridization.

Several of the positive clones that hybridized to the above probe were analyzed for their nucleotide sequences. All of the analyzed clones contained a signal peptide sequence that is considered missing in the reported human MT4-MMP gene; the longest clone was 3.5 kb.

Therefore, it was considered that an mRNA corresponding to the DNA of SEQ ID NO: 3 which can express the 587 amino acid MT4-MMP(2) shown in SEQ ID NO: 1 is expressed in mouse.

EXAMPLE 2. Cloning of Human MT4-MMP (2) Gene

EST clones relating to the human MT4-MMP gene were searched for through databases. However, no clones were registered which contain a sequence encoding a signal peptide as seen in the above-mentioned mouse gene. Therefore, it was considered that secretion-type human MT4-MMP gene does not exist or there are reasons that make the isolation thereof difficult.

A human brain cDNA library (Clontech) was screened using a partial sequence of the mouse MT4-MMP(2) gene, as a probe, from Example 1 encoding an N-terminal region representing the signal peptide. However, the gene of interest could not be isolated. Then, the inventors analyzed 5' regions of transcripts by 5' RACE. For this analysis, monocyte-derived THP-1 (ATCC TIB-202; American Type Culture Collection) cells were used in which expression of MT4-MMP mRNA had been confirmed.

Briefly, a cDNA was prepared using poly(A)$^+$ RNA isolated from human THP-1 cells, a human MT4-MMP selective primer (SEQ ID NO: 9) and Superscript II (Gibco BRL). A single-stranded oligonucleotide adaptor (SEQ ID NO: 10) was ligated to the resultant cDNA with T4 RNA ligase. Then, a PCR was performed in GC buffer using the MT4-MMP selective primer (SEQ ID NO: 9), an adaptor selective primer (SEQ ID NO: 11) and LA Taq (Takara). After completion of this reaction, another PCR was performed using a gene-selective, other primer (SEQ ID NO: 12) and an adaptor selective primer (SEQ ID NO: 13).

The analysis of the 50 clones revealed that, while 3 clones were cDNA fragments containing an MT4-MMP sequence, 47 clones were cDNA fragments encoding a signal peptide sequence similar to that in mouse MT4-MMP(2). From this, in addition to the downstream region of the propeptide sequence already known, the entire region of the mRNA of SEQ ID NO: 4 encoding human MT4-MMP(2) as shown in SEQ ID NO: 2 containing a signal peptide has been elucidated. Although the nucleotide sequence of an EST clone

H97792 was almost identical with the sequence of the MT4-MMP gene reported by Puente [Cancer Research, 56, 944 (1996); SEQ ID NO: 17], a partial sequence of the catalytic domain was different. The EST clone H97792 was more highly conserved with mouse MT4-MMP(2) gene. When the entire sequence of human MT4-MMP(2) gene was determined newly, differences were found even in the previously sequenced region of the MT4-MMP gene reported by Puente.

Mouse and human MT4-MMP(2) genes are mutually conserved well; their propeptide domains, catalytic domains, hinge domains and hemopexin-like domains had 87%, 87%, 78% and 96% homology, respectively. Their signal peptide domains and transmembrane domains had relatively low similarities of 54% and 35%, respectively. When the catalytic domain of human MT4-MMP(2) gene were compared with the catalytic domains of MT1-MMP, MT2-MMP and MT3-MMP, the similarities were 36%, 39% and 31%, respectively. These results also supported that mouse MT4-MMP(2) gene is most close to human MT4-MMP(2) gene. Thus, it was concluded that mouse MT4-MMP(2) gene is a mouse homologue to human MT4-MMP(2) gene.

EXAMPLE 3. Expression of MT4-MMP(2) and Detection of the Gene Product

In order to confirm that a gene product is certainly translated from the isolated cDNA, the cDNA was integrated into pSG5 vector (Stratagene) containing an SV 40 promoter. For detecting the expressed product, a FLAG sequence (Eastman Chemical) was integrated downstream of the latent enzyme processing site to thereby enable detection with anti-FLAG antibodies.

COS-1 cells were transfected with mouse or human MT4-MMP(2) expression plasmids. After 48 hr, cells were harvested and lysed followed by detection of FLAG-labeled MT4-MMP by Western blotting. With the use of an anti-FLAG antibody M2 (Eastman Chemical), a specific 66 kDa band in both cells transfected with the expression plasmids was detected.

EXAMPLE 4. Detection and Analysis of MT4-MMP Transcript

Since MT4-MMP transcript has an *Alu* sequence at 5' end, there was a possibility that it

contains intron(s). Using a partial sequence of human MT4-MMP(2) (positions 212-519 of SEQ ID NO: 4) as a probe, hybridized clones were isolated from a library of Health Science Research Resources Bank (Deposit No. LI020) by hybridization, and plasmids were extracted from the resultant clones by conventional methods. Then, the present inventors examined nucleotide sequences around the 5' end region (positions 140-272 of SEQ ID: 17) of MT4-MMP contained in these plasmids.

When MT4-MMP gene was compared with MT4-MMP(2) gene, MT4-MMP nucleotide sequence of the region in which homology no longer exists (positions 1-139 of SEQ ID NO: 17) was almost identical with positions 3008-3147 of the genomic sequence (SEQ ID NO: 18); and a splice donor sequence was found on the border between the region with homology and the region without homology. The sequence encoding the exons of MT4-MMP (positions 140-340 of SEQ ID NO: 17) were almost identical with positions 3148-3280 and positions 3564-3633 of the genomic sequence (SEQ ID NO: 18). From these results, it was concluded that the transcript still containing the first intron is MT4-MMP transcript.

From these results, it was considered that two mRNAs encoding MT4-MMP and MT4-MMP(2) are expressed in human.

In order to discriminate these two transcripts by performing RT-PCR separately, 5' primers specific to individual transcripts (MT4-MMP: SEQ ID NO: 14; MT4-MMP(2): SEQ ID NO: 15) and a common 3' primer (SEQ ID NO: 16) were prepared.

The expression of these transcripts in various cancer cells is shown in Table 1 below.

Table 1. Expression of MT4-MMP(2) and MT4-MMP Transcripts in Cancer Cells

Cancer Cell Line	MT4-MMP(2)	MT4-MMP	Accession Number
Jurkat (T cell)	++	+/-	ATCC TIB-152
Raji (B cell)	-	-	ATCC CCL-86
BJAB (B cell)	-	-	ATCC HB-136
THP-1 (monocytic)	++	+	ATCC TIB-202
K562 (monocytic)	++	-	ATCC CCL-243
U-937 (monocytic)	++	-	ATCC CRL-1593.2
U-251 MG (astrocytoma)	++	-	Hakkoken IFO50288
SK-N-SH (neuroblastoma)	++	-	ATCC HTB-11
no.10 (glioma)	+/-	-	Hakkoken IFO50368
KALS-1 (glioma)	++	-	Hakkoken IFO50434
MKN-7 (gastric)	+	-	Riken RCB0999
MKN-28 (gastric)	-	-	Riken RCB1000
NUGC-4 (gastric)	+	-	HS Found JCRB0834
PANC-1 (pancreatic)	++	+	ATCC CRL-1469
MIA PaCa-2 (pancreatic)	++	+/-	ATCC CRL-1420
SK-HEP-1 (hepatoma)	++	+	ATCC HTB-52
Hep 3B (hepatoma)	++	+	ATCC HB-8064
ZR-75-1 (breast)	++	+	ATCC CRL-1500
MCF7(adenocarcinoma)	++	+	ATCC HTB-22
T-24 (bladder)	++	+	ATCC HTB-4
A375 (melanoma)	++	+	ATCC CRL-1619
HT-1080 (fibrosarcoma)	+	-	ATCC CCL-121

++: strong expression; +: medium expression; +/-: slight expression; -: no expression

ATCC: American Type Culture Collection

HS Found.: Japan Health Sciences Foundation

Riken: The Institute of Physical and Chemical Research

Hakkoken: Institute for Fermentation, Osaka

MT4-MMP was only expressed in those cells where expression of MT4-MMP(2) was recognized.

From these results, it is believed that MT4-MMP(2) is the major transcript and that expression of MT4-MMP also occurs depending on cells under similar transcriptional control.

EXAMPLE 5. Expression of MT4-MMP(2) in mouse Tissues

Tissues of 4-week old mice were excised by organ. RNA was extracted therefrom and used to examine the expression pattern of MT4-MMP(2). Briefly, 20 μg of total RNA was electrophoresed on 1% agarose gel and transferred onto a nylon membrane followed by Northern blot analysis using ^{32}P-labeled mouse MT4-MMP(2) gene as a probe, to thereby examine the expression pattern of MT4-MMP(2).

Organs in which particularly high expression was observed were the cerebrum, cerebellum, brainstem, large intestine, uterus, and testis. Little expression was observed in the adrenal, mammary gland, and placenta. The results of expression in mouse were consistent with the results of MT4-MMP expression in human tissues reported by Puente et al. [Cancer Research, 56, 944 (1996)].

In mouse, the expression of MT4-MMP(2) was very high in the brain, and its expression was also observed in some limited organs such as the large intestine, uterus and testis. This presents a contrast to the expression of MT1-MMP and MT2-MMP seen in a relatively wide range of tissues. From this, it is believed that MT4-MMP(2) is involved in the maintenance of homeostasis in tissues through the degradation of extracellular substrates specific to those organs expressing MT4-MMP(2).

EXAMPLE 6. Expression of a Mouse MT4-MMP(2) Partial Peptide (Hemopexin-like Domain) in *E. coli*

A cDNA encoding a mouse MT4-MMP(2) partial peptide (hemopexin-like domain) having an amino acid sequence represented by positions 321-550 of SEQ ID NO: 1 to which a

methionine residue was added at the N-terminus was amplified by polymerase chain reaction (PCR) using the cDNA of mouse MT4-MMP(2) as a template.

The amplified fragment was subcloned into an *E. coli* expression vector pET3a (Takara) and then introduced into *E. coli* BL21 (DE3) pLysS (Takara). This *E. coli* was grown in 1 liter of expression medium in the presence of 100 μg/ml of ampicillin until OD_{600} reached 0.5. Then, the cells were stimulated with 0.4 mmol/L of isopropyl- β -D-thiogalactopyranoside (IPTG) and cultured for another three hours.

After the culturing, granules (inclusion bodies) consisting of the mouse MT4-MMP(2) partial peptide formed in *E. coli* cells were collected by conventional methods and dissolved in a solubilization solution containing 8 mol/L urea, 50 mmol/L Tris-HCl (pH 8.6) and 20 mmol/L dithiothreitol (DTT). The resultant solution was applied to High Q anion exchange column followed by recovery of the fraction eluted with 0.2 mol/L sodium chloride.

This fraction was diluted with a solution containing 50 mmol/L Tris-HCl (pH 8.6), 6 mol/L urea, 1 mmol/L dithiothreitol, 0.15 mol/L sodium chloride, 5 mmol/L calcium chloride, 100 mmol/L zinc chloride and 0.02% sodium azide. Then, cystamine (final concentration: 20 mmol/L) was added to the resultant dilution. Subsequently, the resultant solution was dialyzed against a solution containing 50 mmol/L Tris-HCl (pH 8.6), 0.15 mol/L sodium chloride, 5 mmol/L calcium chloride, 100 mmol/L zinc chloride, 5 mmol/L β mercaptoethanol, 1 mmol/L 2-hydroxyethyldisulfide and 0.02% sodium azide at 4℃. Further, dialysis was performed against 10 volumes of a solution containing 50 mmol/L Tris-HCl (pH 7.5), 0.15 mol/L sodium chloride, 5 mmol/L calcium chloride, 50 mmol/L zinc chloride and 0.02% sodium azide (4 hr x 3 times). The dialyzed solution was centrifuged at 22,000xg at 4℃ for 10 min to remove the precipitate.

The supernatant was applied to S-200 column pre-equilibrated with a buffer containing 50 mmol/L Tris-HCl (pH 7.5), 150 mmol/L sodium chloride, 10 mmol/L calcium chloride and 0.02% sodium azide for gel filtration to obtain a mouse MT4-MMP(2) partial peptide corresponding to the hemopexin-like domain.

EXAMPLE 7. Expression of a Human MT4-MMP(2) Partial Peptide (Propeptide Domain +

Active Domain) in *E. coli*

A cDNA encoding a human MT4-MMP(2) partial peptide having an amino acid sequence represented by positions 58-298 of SEQ ID NO: 2 was amplified by polymerase chain reaction (PCR) using the cDNA of human MT4-MMP(2) as a template.

The amplified fragment was subcloned into an *E. coli* expression vector pRSET (Invitrogen). The enzyme was expressed as a fusion protein fused to the 6x His sequence present in the pRSET-derived leader sequence. This vector was introduced into *E. coli* BL21 (DE3) pLysS (Takara). This *E. coli* was grown in 1 liter of expression medium (tryptone, 12 g/L; yeast extract, 24 g/L; sodium chloride, 10 g/L; Trisma base, 250 mg/L; glycerol, 4 ml/L) in the presence of 100 μg/ml ampicillin until OD_{600} reached 0.5. Then, the cells were stimulated with 0.4 mmol/L isopropyl-β-D-thiogalactopyranoside (IPTG) and cultured for another three hours.

After the culturing, granules (inclusion bodies) consisting of the human MT4-MMP(2) partial peptide (propeptide domain + active domain) formed in *E. coli* cells were collected by conventional methods and dissolved in a solubilization solution containing 8 mol/L urea and 50 mmol/L Tris-HCl (pH 8.6). The resultant solution was applied to a nickel chelate column followed by recovery of the fraction eluted with 250 mmol/L imidazole.

This fraction was diluted with a solution containing 50 mmol/L Tris-HCl (pH 8.6), 6 mol/L urea, 20 mmol/L dithiothreitol, 0.15 mol/L sodium chloride, 100 mmol/L calcium chloride, 100 μmol/L zinc chloride and 0.02% sodium azide (200-fold dilution). Then, cystamine (final concentration: 20 mmol/L) was added to the resultant dilution. Subsequently, the resultant solution was dialyzed against a solution containing 50 mmol/L Tris-HCl (pH 8.6), 0.15 mol/L sodium chloride, 10 mmol/L calcium chloride, 100 μmol/L zinc chloride, 5 mmol/L βmercaptoethanol, 1 mmol/L 2-hydroxyethyldisulfide and 0.02% sodium azide at 4℃. Further, dialysis was performed against 10 volumes of a solution containing 50 mmol/L Tris-HCl (pH 7.5), 0.15 mol/L sodium chloride, 10 mmol/L calcium chloride, 50 μmol/L zinc chloride and 0.02% sodium azide (4 hr x 3 times). The thus dialyzed solution was centrifuged at 22,000xg at 4℃ for 10 min to remove the precipitate.

The supernatant obtained was concentrated 5-fold with Amicon YM-10 (Millipore) to

prepare a crude enzyme.

EXAMPLE 8. Measurement of the Activity of the Human MT4-MMP(2) Partial Peptide (Active Domain)

a) Activation of the Human MT4-MMP(2) Partial Peptide (Propeptide Domain + Active Domain)

It is known that MMPs are activated by trypsin treatment and then exhibit metalloproteinase activity. Whether MT4-MMP(2) is also activated by such treatment or not was examined by the method described below.

Briefly, trypsin (Wako Purechemical Industries, Ltd.) was added to 200 μl of the crude MT4-MMP(2) partial peptide (propeptide domain + active domain) solution to give a concentration of 0.1 μg/ml, and reacted at 37℃ for 30 min. Then, phenylmethanesulfonyl fluoride (PMSF) (a serine protease inhibitor) was added to the reaction solution at 1 mmol/L to inactivate the trypsin.

b) Assay

To 10 μl of the activated enzyme, a measurement buffer or an inhibitor diluted with a measurement buffer (TIMP-1 or TIMP-2; final concentration: 1 μg/ml) was added to make a 50 μl solution. To this solution, 50 μl of 10 μmol/L fluorescent substrate was added and reacted at 37℃ for 120 min. After the completion of each reaction, fluorescence generated by the enzyme reaction was measured. Measurement was carried out under the following conditions: excitation wave length: 320 nm; fluorescence wave length: 395 nm.

The reagents and substrates used in this assay were as described below.

Fluorescent substrate: DMSO stock (10 mmol/L); MOCAc-Pro-Leu-Gly-Leu-A_2pr(Dnp)-Ala-Arg-NH_2 (Peptide Institute, Inc.)

Standard fluorescent substrate: DMSO stock (1 mmol/L); MOCAc-Pro-Leu-Gly (Peptide Institute, Inc.)

Activity measurement buffer: 0.1 mol/L Tris-HCl (pH 7.5; Nacalai Tesque), 0.1 mol/L NaCl (Nacalai Tesque), 0.01 mol/L $CaCl_2$ (Wako Purechemical), 0.05% Briji-35 (w/v; Wako Purechemical)

The results of the measurement are shown in Table 2. Similar to other MMPs, the MT4-MMP(2) partial peptide, in particular, the partial peptide after the activation by trypsin exhibited a strong substrate-degrading activity.

It is reported that MT-MMPs are not inhibited by the metalloproteinase inhibitor TIMP-1, but inhibited by TIMP-2 [FEBS Letters, 393, 101 (1996)].

Whether MT4-MMP(2) also has such a nature or not was examined.

As shown in Table 2, similar to the activities of other MT-MMPs, the activity of MT4-MMP(2) was not inhibited by TIMP-1, but strongly inhibited by TIMP-2.

These results revealed that MT4-MMP(2) is one type of MT-MMP.

Table 2. Measurement of the Activity of Human MT4-MMP(2) Partial Peptide (Active Domain)

Sample	Trypsin Treatment	Inhibitor	Fluorescence Intensity (Mean±SD) (n=3)
Blank			0.000±0.057
Human MT4-MMP(2) partial peptide	-	None	1.304±0.056
Human MT4-MMP(2) partial peptide	+	None	4.882±0.102
Human MT4-MMP(2) partial peptide	+	TIMP-1	3.493±0.166
Human MT4-MMP(2) partial peptide	+	TIMP-2	0.076±0.065

EXAMPLE 9. Cloning of Mouse MT5-MMP Gene

In order to isolate mouse MT5-MMP gene, a brain cDNA library from mouse 17-day embryo was prepared using ZAP-cDNA Synthesis Kit (Stratagene) according to the manual attached to the kit.

The resultant cDNA library was screened by plaque hybridization using human MT3-MMP gene as a probe. Clones exhibiting a strong signal and clones exhibiting a weak signal were obtained. The nucleotide sequences of these clones were determined.

As a result of analysis of clones with a weak signal, a 2.1 kb sequence was found in one of them. Although this sequence exhibited weak homology to human and rat MT3-MMP genes, it was not homologous to other MMP genes. Thus, it was considered that this sequence represents a novel MMP gene.

Subsequently, a 3.7 kb cDNA fragment that hybridized to the above-described 2.1 kb sequence was obtained from the above library by plaque hybridization. From the 2.1 kb and 3.7 kb sequences, a 4.2 kb cDNA sequence shown in SEQ ID NO: 7 was obtained.

A protein with 618 amino acids represented by SEQ ID NO: 5 was encoded in the cDNA shown in SEQ ID NO: 7. Since the peptide of SEQ ID NO: 5 contains those sequences corresponding to the individual domains of MT-MMPs in well-conserved states, it was concluded that this peptide is a novel MT-MMP, namely, mouse MT5-MMP (Fig. 1).

EXAMPLE 10. Cloning of Human MT5-MMP Gene

In order to confirm the human gene corresponding to mouse MT5-MMP gene, a human kidney cDNA library (Clontech) was screened by plaque hybridization using mouse MT5-MMP gene as a probe in the same manner as in Example 9. As a result, a gene that has 92% homology to mouse MT5-MMP gene and is different from known MT-MMP genes was obtained.

All of the sequenced human MT5-MMP cDNA clones lacked a 5' region that is supposed to encode a signal peptide. Thus, the sequence of the missing region was determined by 5' RACE as described below to thereby determine the nucleotide sequence containing the entire region encoding human MT5-MMP gene.

Briefly, cDNA was prepared from a human brain poly(A)$^+$ RNA (Clontech) using Superscript II (Gibco BRL) and a human MT5-MMP gene-selective primer (SEQ ID NO: 19) according to the manual attached to the kit.

A single-stranded oligonucleotide adaptor (SEQ ID NO: 10) was ligated to the resultant cDNA with T4 RNA ligase. Then, the cDNA was subjected to PCR in GC buffer using the MT5-MMP gene-selective primer (SEQ ID NO: 19), an adaptor-selective primer (SEQ ID NO: 11) and LA Taq (Takara).

After completion of the above PCR, another PCR was performed using an other gene-selective primer (SEQ ID NO: 20) and an adaptor-selective primer (SEQ ID NO: 13). From the above-mentioned sequence obtained from the human kidney cDNA library using the mouse gene as a probe and the sequence obtained from the 5' RACE, a 2.6 kb cDNA fragment

(shown in SEQ ID NO: 8) that encodes a 645 amino acid protein (shown in SEQ ID NO: 6) was obtained.

EXAMPLE 11. Expression of MT5-MMP mRNAs in Internal Organs

Expression of MT5-MMP gene in tissues was examined by Northern blotting.

Briefly, 20 μg of total RNA was electrophoresed on 1% agarose gel and transferred onto a nylon membrane. Then, Northern blotting was carried out using ^{32}P-labeled mouse MT5-MMP gene as a probe to examine the expression pattern of approximately 4 kb MT5-MMP mRNAs.

In 2-week old mice, a strong expression was observed only in the brain, but the expression was around detection limit or below in other tissues of other organs.

When expression in human tissues was examined with Multiple Tissue Blot (Clontech) using human MT5-MMP gene as a probe, high expression was observed in the brain. The results of Northern blotting using ^{32}P-labeled human MT5-MMP gene as a probe revealed that strong expression of both 4.0 kb and 4.8 kb MT5-MMP mRNAs are also recognized in the human brain. In human, the expression was also recognized in the kidney and pancreas. The 4.8 kb mRNA and the 4.0 kb mRNA were expressed strongly in the brain and in the kidney and pancreas, respectively.

Then, RT-PCR was carried out using MT5-MMP specific primers (SEQ ID NOS: 21 and 22) to analyze these fragments. As a result, it was found that a DNA fragment of the same size as that of the fragment amplified in the brain is amplified in the kidney and pancreas with almost equal efficiencies and that no products of different sizes were found. Thus, it was believed that the shorter transcript contains the entire coding region.

When the expression of MT5-MMP in mouse and human was examined, characteristic expression was observed in the brain. In particular, the expression was limited in the brain in mouse, and was very low in other internal organs.

Since the expression of this gene in the brain is characteristic, site-specific expression was examined using Human Brain Multiple Tissue Blot (Clontech).

High expression of MT5-MMP was observed in the cerebellum. Its expression was

also observed in the cerebral cortex, medulla, occipital region of head, frontal region of head, temporal region of head and putamen, but not observed in the spinal cord.

These results show a remarkable characteristic of MT5-MMP gene different from other MT-MMP genes expressed in various tissues.

In human, the expression of MT5-MMP was ~~also~~ strong in the brain, and its expression was observed in the kidney and pancreas. The results of examination of its site-specific expression in the human brain revealed a characteristic expression in the cerebellum. High expression in the cerebellum was also confirmed in mouse.

These results suggest the possibility that MT5-MMP controls the degradation of extracellular matrixes around cells associated with such processes as the maturation and maintenance of brain tissues, the construction of nervous network, and so forth.

EXAMPLE 12. Expression of MT5-MMP mRNA in Cancer Cells

MT1-MMP is expressed frequently in cancer cells *per se* and interstitial cells around them in many cancer tissues and functions as an activator of gelatinase A at the tissue level. The expression of MT5-MMP in various cancer cell strains was examined by RT-PCR using MT5-MMP-specific primers (SEQ ID NOS: 21 and 22).

The results are shown in Table 3 below.

Table 3. Expression of MT5-MMP Transcript in Cancer Cells

Cancer Cell Line	MT5-MMP	Accession Number
Jurkat (T cell)	-	ATCC TIB-152
Raji (B cell)	-	ATCC CCL-86
BJAB (B cell)	-	ATCC HB-136
THP-1 (monocytic)	-	ATCC TIB-202
K562 (monocytic)	-	ATCC CCL-243
U-937 (monocytic)	-	ATCC CRL-1593.2
U-251 MG (astrocytoma)	-	Hakkoken IFO50288
SK-N-SH (neuroblastoma)	+++	ATCC HTB-11
no.10 (glioma)	++	Hakkoken IFO50368
KALS-1 (glioma)	+++	Hakkoken IFO50434
MKN-7 (gastric)	+	Riken RCB0999
MKN-28 (gastric)	-	Riken RCB1000
NUGC-4 (gastric)	+	HS Found JCRB0834
PANC-1 (pancreatic)	+	ATCC CRL-1469
MIA PaCa-2 (pancreatic)	+	ATCC CRL-1420
SK-HEP-1 (hepatoma)	+	ATCC HTB-52
Hep 3B (hepatoma)	+	ATCC HB-8064
ZR-75-1 (breast)	?	ATCC CRL-1500
MCF7(adenocarcinoma)	-	ATCC HTB-22
T-24 (bladder)	-	ATCC HTB-4
A375 (melanoma)	+/-	ATCC CRL-1619
HT-1080 (fibrosarcoma)	+/-	ATCC CCL-121

+++: very strong expression; ++: strong expression; +: medium expression; +/-: slight expression; -: no expression

ATCC: American Type Culture Collection

HS Found.: Japan Health Sciences Foundation

Riken: The Institute of Physical and Chemical Research

Hakkoken: Institute for Fermentation, Osaka

While MT1-MMP is expressed in various cancer cell lines, cell lines expressing MT5-MMP were specific in the nervous system-derived neuroblastoma [SK-N-SH (HTB-11, ATCC)], undifferentiated glioma [no. 10 (IFO50368, Institute for Fermentation, Osaka)], and glioma [KALS-1, (IFO50434, Institute for Fermentation, Osaka)], with the correlation of the expression in brain.

Also, its expression in pancreatic cancer cell strains [PANC-1 (CRL-1469, ATCC); MIA PaCa-2 (CRL-1420, ATCC)] and hepatoma cell strains [SK-HEP-1 (HTB-52, ATCC): Hep 3B (HB-8064, ATCC)] was characteristic.

It is considered that abnormal expression of MT-MMPs on cell surfaces promotes the infiltration of cells. Actually, excessive expression of MT1-MMP enhances the infiltrating ability of cancer cell lines and increases the frequency of experimental metastasis. In human cancer tissues, cancer cells and fibroblasts around them express MT1-MMP at high frequency, and the presence of gelatinase A which MT1-MMP activates at sites of its expression is well correlated with the infiltration and metastasis of cancer.

Since MT5-MMP is expressed in undifferentiated glioma, glioma, pancreatic cancer and hepatoma cell lines, the possibility has been suggested that excessive expression of MT5-MMP is involved in the malignant nature of cancer cells in a specific types of cancers.

EXAMPLE 13. Expression of a Mouse MT5-MMP Partial Peptide (Propeptide Domain + Active Domain) in *E. coli*

A cDNA encoding a mouse MT5-MMP partial peptide having an amino acid sequence represented by positions 40-300 of SEQ ID NO: 5 to which a methionine residue is added at the N terminus was amplified by polymerase chain reaction (PCR) using the cDNA of mouse MT5-MMP as a template.

The amplified fragment was subcloned into an *E. coli* expression vector pET3a (Takara)

and then introduced into *E. coli* BL21 (DE3) pLysS (Takara). This *E. coli* was grown in 1 liter of expression medium (12 g/L of tryptone; 24 g/L of yeast extract; 10 g/L of sodium chloride; 250 mg/L of Trisma base; 4 ml/L of glycerol) in the presence of 100 μg/mL ampicillin until OD_{600} reached 0.5. Then, the cells were stimulated with 0.4 mmol/L isopropyl-β-D-thiogalactopyranoside (IPTG) and cultured for another three hours.

After the culturing, granules (inclusion bodies) consisting of the mouse MT5- MMP partial peptide formed in the *E. coli* cells were recovered by conventional methods and dissolved in a solubilization solution containing 8 mol/L urea, 50 mmol/L Tris-HCl (pH 8.6) and 20 mmol/L dithiothreitol (DTT). The resultant solution was applied to Q-anion ion exchange column followed by recovery of the fraction eluted with 0.1 M NaCl.

This fraction was diluted with a solution containing 50 mmol/L Tris-HCl (pH 8.6), 6 mol/L urea, 1 mmol/L dithiothreitol, 0.15 mol/L sodium chloride, 5 mmol/L calcium chloride, 100 mmol/L zinc chloride and 0.02% sodium azide. Then, cystamine (final concentration: 20 mmol/L) was added to the resultant dilution. Subsequently, the resultant solution was dialyzed against 4 L of a solution containing 50 mmol/L Tris-HCl (pH 8.6), 0.15 mol/L sodium chloride, 5 mmol/L calcium chloride, 100 mmol/L zinc chloride, 5 mmol/L β mercaptoethanol, 1 mmol/L 2-hydroxyethyldisulfide and 0.02% sodium azide at 4℃ overnight. Further, dialysis was performed against 10 volumes of a solution containing 50 mmol/L Tris-HCl (pH 7.5), 0.15 mol/L sodium chloride, 5 mmol/L calcium chloride, 50 μ mol/L zinc chloride and 0.02% sodium azide (4 hr x 3 times). The thus dialyzed solution was centrifuged at 22,000xg at 4℃ for 10 min to remove the precipitate.

The supernatant obtained was concentrated with Amicon YM-10 (Millipore) and treated with 0.1 μg/ml trypsin at 37℃ for 30 min. After inactivation of the trypsin with 1 mmol/L DTT, the sample was applied to S-200 column pre-equilibrated with a buffer containing 50 mmol/L Tris-HCl (pH 7.5), 150 mmol/L sodium chloride, 10 mmol/L calcium chloride and 0.02% sodium azide to perform gel filtration. As a result, the mouse MT5-MMP partial peptide (propeptide domain + active domain) was obtained.

Human MT5-MMP peptide can also be expressed in the same manner.

EXAMPLE 14. Measurement of the Activity of Mouse MT5-MMP Partial Peptide (Active Domain)

ProMMP-2 (final concentration: 1 μg/mL) and the mouse MT5-MMP partial peptide (propeptide domain + active domain) (final concentration: 1 μg/mL) were mixed and incubated at 37℃ for 1 hr. In this operation, Briji 35-added TNC buffer [50 mmol/L Tris-HCl (pH 7.5), 150 mmol/L NaCl, 10 mmol/L $CaCl_2$, 0.02% NaN_3, 0.05% Briji 35] was used. After the incubation, an equal volume of SDS/PAGE loading buffer was added to the sample, which was then electrophoresed and subjected to Coomassie staining according to routine procedures. As a positive control of activation for ProMMP-2, p-aminophenylmercuric acetate (APMA) was used. As a result, activation of ProMMP-2 was recognized depending on a MMP concentration. The results are shown in Fig. 2.

INDUSTRIAL APPLICABILITY

By using the DNA of novel MT4-MMP(2) polypeptide obtained by the present invention, it becomes possible to diagnose, prevent or treat diseases such as arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, wounds including corneal ulcer, leukemia, cancer, and inflammations associated with infiltration of leukocytes.

Furthermore, by using the DNA of novel MT5-MMP polypeptide obtained by the present invention, it becomes possible to diagnose, prevent or treat diseases such as arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, wounds including corneal ulcer, leukemia, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease, brain tumor, cancer, and inflammations associated with infiltration of leukocytes.

CLAIMS

1. A polypeptide consisting of the amino acid sequence as shown in SEQ ID NO: 1.

2. A polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence of the polypeptide of claim 1 and having metalloproteinase activity.

3. A polypeptide consisting of the amino acid sequence as shown in SEQ ID NO: 2.

4. A polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence of the polypeptide of claim 3 and having metalloproteinase activity.

5. A polypeptide consisting of the amino acid sequence as shown in SEQ ID NO: 5.

6. A polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence of the polypeptide of claim 5 and having metalloproteinase activity.

7. A polypeptide consisting of the amino acid sequence as shown in SEQ ID NO: 6.

8. A polypeptide having an amino acid sequence wherein one or several amino acids are deleted, substituted or added in the amino acid sequence of the polypeptide of claim 7 and having metalloproteinase activity.

9. A DNA encoding the polypeptide of any one of claims 1 to 4.

10. A DNA encoding the polypeptide of any one of claims 5 to 8.

11. A DNA consisting of the nucleotide sequence of positions 86-1846 of SEQ ID NO: 3 or positions 100-1917 of SEQ ID NO: 4, or a DNA which hybridizes to said DNA under stringent conditions and which encodes a polypeptide having metalloproteinase activity.

12. A DNA consisting of the nucleotide sequence of positions 75-1928 of SEQ ID NO: 7 or positions 1-1935 of SEQ ID NO: 8, or a DNA which hybridizes to said DNA under stringent conditions and which encodes a polypeptide having metalloproteinase activity.

13. A recombinant DNA that is obtained by integrating the DNA of any one of claims 9 to 12 into a vector.

14. A transformant comprising the recombinant DNA of claim 13.

15. The transformant of claim 14, wherein said transformant is a microorganism belonging to the genus *Escherichia.*

16. The transformant of claim 15, wherein said microorganism belonging to the genus *Escherichia* is *Escherichia coli.*

17. A method of producing the polypeptide of any one of claims 1 to 8, comprising culturing a transformant comprising a recombinant DNA obtained by integrating a DNA encoding said polypeptide into a vector in a medium, allowing said polypeptide to be produced and accumulated in the resultant culture, and recovering said polypeptide from said culture.

18. An oligonucleotide selected form an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 9 or 11; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the

above oligonucleotides.

19. An oligonucleotide selected form an oligonucleotide having a nucleotide sequence identical with a nucleotide sequence consisting of consecutive 5 to 60 bases of the DNA of claim 10 or 12; an oligonucleotide having a nucleotide sequence complementary to the nucleotide sequence of said oligonucleotide; or an oligonucleotide derivative of any one of the above oligonucleotides.

20. A method of detecting an mRNA encoding the polypeptide of any one of claims 1 to 8 using the oligonucleotide of claim 18 or 19.

21. A method of inhibiting expression of the polypeptide of any one of claims 1 to 8 using the oligonucleotide of claim 18 or 19.

22. A method of screening for an inhibitor or an activator of the polypeptide of any one of claims 1 to 8, which comprises using the polypeptide and a cell that expresses the polypeptide.

23. A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said agent comprises the polypeptide of any one of claims 1 to 4.

24. A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes,

brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said agent comprises the polypeptide of any one of claims 5 to 8.

25. A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said agent comprises the DNA of claim 9 or 11.

26. A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said agent comprises the DNA of claim 10 or 12.

27. A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said agent comprises the oligonucleotide of claim 18.

28. A diagnostic agent, therapeutic agent or prophylactic agent for arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact

dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said agent comprises the oligonucleotide of claim 19.

29. A vector for gene therapy for treating arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury or inflammations associated with infiltration of leukocytes, wherein said vector is obtained by integrating the DNA of claim 9 or 11, or the oligonucleotide of claim 18 into a vector.

30. A vector for gene therapy for treating arthrosis deformans, rheumatoid arthritis, asthma, autoimmune diseases, atopic dermatitis, psoriasis, contact dermatitis, alopecia, ischemic heart diseases, immune response associated with organ transplantation, hepatitis, nephritis, pancreatitis, arteriosclerosis, leukemia, malignant tumor, wounds, corneal ulcer, tissue injury, inflammations associated with infiltration of leukocytes, brain disorders at the time of cerebral apoplexy, Alzheimer's disease, dementia, multiple sclerosis, Parkinson's disease or brain tumor, wherein said vector is obtained by integrating the DNA of claim 10 or 12, or the oligonucleotide of claim 19 into a vector.

31. A method of screening for a compound that regulates the expression of a gene encoding the polypeptide of any one of claims 1 to 8, which comprises contacting a cell that expresses the polypeptide with a test sample.

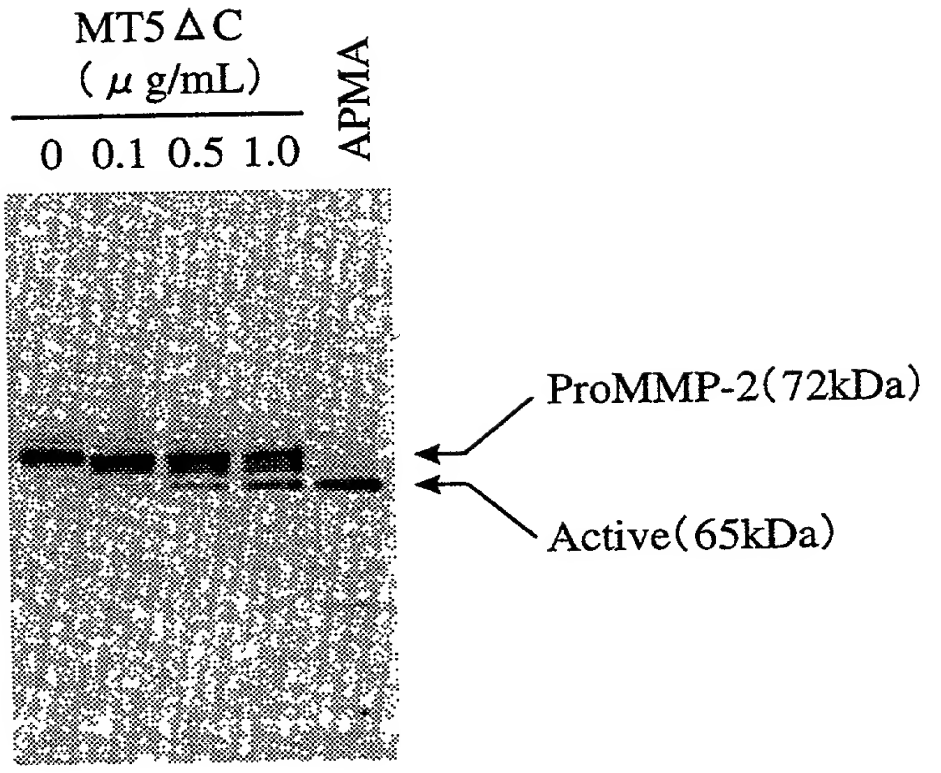
32. The method of claim 31, wherein said compound that regulates the expression of a gene is detected by determining the amount of mRNA encoding the polypeptide of any one of

claims 1 to 8.

Fig. 1

```
human MT1-MMP      1 ----MSPAP----RP------------------SRCLLLPL-LTLGTALASLGSAQS----------------------SSFSPEAWLQQYGYLPPGD  49
human MT2-MMP      1 ----MGSDPSAPGRPGWT------GSLLGDREEAARPRLLPL-LLVLLGCLGLGVAAED--------------------AEVHAENWLRLYGYLPQPS  67
human MT3-MMP      1 -MILLTFSTGRRLDFVH----------------HSGVFFLQT-LLWILCATVCG----------------------TEQYFNVEVWLQKYGYLPPTD  57
human MT4-MMP(2)   1 MRRRAARGPGPP-PPGP--------------GLSRLPLLPLPLLLLLALGTRGGCAAPEPAR--------------RAEDLSLGVEWLSRFGYLPPAD  69
human MT5-MMP      1 ----MPRSRGGRAAPGPPPPPPPPGQAPRWSRWRVPGRLLLL-LLPALCCLPGAARAAAAAAGAGNRAAVAVAVARADEAEAPFAGQNWLKSYGYLLPYD  95
mouse MT5-MMP      1 ----MPRSRGGRAAPG---------QASRWSGWRAPGRLLP--LLPALCCLAAAAGAGKPAG----------------ADAPFAGQNWLKSYGYLLPYE  68
                                                 *   *                                                 **  .***

human MT1-MMP     50 LRTHTQRSPQSLSAAIAAMQKFYGLQVTGKADADTMKAMRRPRCGVPDKFGAEIKANVRR--KRYAIQGLKWQHNEITFCIQNYT--PKVGEYATYEAIR 145
human MT2-MMP     68 RHMSTMRSAQILASALAEMQRFYGIPVTGVLDEETKEWMKRPRCGVPDQFGVRVKANLRRRRKRYALTGRKWNNHHLTFSIQNYT--EKLGWYHSMEAVR 165
human MT3-MMP     58 PRMSVLRSAETMQSALAAMQQFYGINMTGKVDRNTIDWMKKPRCGVPDQTRGSSKFHIRR--KRYALTGQKWQHKHITYSIKNVT--PKVGDPETRKAIR 153
human MT4-MMP(2)  70 PTTGQLQTQEELSKAITAMQQFGGLEATGILDEATLALMKTPRCSLPDLPVLTQ---ARR--RRQAPAPTKWNKRNLSWRVRTFPRDSPLGHDTVRALMY 164
human MT5-MMP     96 SRASALHSAKALQSAVSTMQQFYGIPVTGVLDQTTIEWMKKPRCGVPDHPHLSR--RRRN--KRYALTGQKWRQKHITYSIHNYT--PKVGELDTRKAIR 189
mouse MT5-MMP     69 SRASALHSGKALQSAVSTMQQFYGIPVTGVLDQTTIEWMKKPRCGVPDHPHLSR--RRRN--KRYALTGQKWRQKHITYSIHNYT--PKVGELDTRKAIR 162
                        ..   .  *.. **.* *.  **  *  *   *. *** .**         *   .* *    **    ..  ...     .*      .

human MT1-MMP    146 KAFRVWESATPLRFREVPYAYIREGHEKQADIMIFFAEGFHGDSTPFDGEGGFLAHAYFPGPN-IGGDTHFDSAEPWTVRNEDLNGNDIFLVAVHELGHA 244
human MT2-MMP    166 RAFRVWEQATPLVFQEVPYEDIRLRRQKEADIMVLFASGFHGDSSPFDGTGGFLAHAYFPGPG-LGGDTHFDADEPWTFSSTDLHGNNLFLVAVHELGHA 264
human MT3-MMP    154 RAFDVWQNVTPLTFEEVPYSELENGK-RDVDITIIFASGFHGDSSPFDGEGGFLAHAYFPGPG-IGGDTHFDSDEPWTLGNPNHDGNDLFLVAVHELGHA 251
human MT4-MMP(2) 165 YALKVWSDIAPLNFHEV------AGS--TADIQIDFSKADHNDGYPFDARR-HRAHAFFPGHHHTAGYTHFNDDEAWTFRSSDAHGMDLFAVAVHEFGHA 255
human MT5-MMP    190 QAFDVWQKVTPLTFEEVPYHEIKSDR-KEADIMIFFASGFHGDSSPFDGEGGFLAHAYFPGPG-IGGDTHFDSDEPWTLGNANHDGNDLFLVAVHELGHA 287
mouse MT5-MMP    163 QAFDVWQKVTPLTFEEVPYHEIKSDR-KEADIMIFFASGFHGDSSPFDGEGGFLAHAYFPGPG-IGGDTHFDSDEPWTLGNANHDGNDLFLVAVHELGHA 260
                      *  **   .** * **            ** . *.   *.*  ***      ***.***     * ***   * **       *  .* ***** ***

human MT1-MMP    245 LGLEHSSDPSAIMAPFYQWMDTE--NFVLPDDDRRGIQQLYGGESG-------FPTKMPPQP------RTTSRPSVPDKPKNP---------------- 312
human MT2-MMP    265 LGLEHSSNPNAIMAPFYQWKDVD--NFKLPEDDLRGIQQLYGTPDGQPQPTQPLPTVTPRRPG-----RPDHRPPRPPQPPPPGGKPERPPKPGPPVQPR 357
human MT3-MMP    252 LGLEHSNDPTAIMAPFYQYMETD--NFKLPNDDLQGIQKIYGPPDKIPPPTRPLPTVPPHRSIPPADPRKNDR-PKPPRPPTG---------------- 331
human MT4-MMP(2) 256 IGLSHVAAAHSIMRPYYQGPVGDPLRYGLPYEDKVRVWQLYGVRESVSPTAQ--PEEPPLLPE-----PPDNRSSAPPRKD---------------- 329
human MT5-MMP    288 LGLEHSSDPSAIMAPFYQYMETH--NFKLPQDDLQGIQKIYGPPAEPLEPTRPLPTLPVRRIHSPSE-RKHERQPRPPRPPLGD---------------- 368
mouse MT5-MMP    261 LGLEHSNDPSAIMAPFYQYMETH--NFKLPQDDLQGIQKIYGPPAEPLEPTRPLHTLPVRRIHSPSE-RKHERHPRPPRPPLGD---------------- 341
                      .** *     .** *.**        . ** .*   . ..**                                  *   * .

human MT1-MMP    313 ------TYGPNICDGNFDTVAMLRGEMFVFKKRWFWRVRNNQ-VMDGYPMPIGQFWRGLP---ASINTAYER-KDGKFVFFKGDKHWVFDEASLEPGYPK 401
human MT2-MMP    358 ATERPDQYGPNICDGDFDTVAMLRGEMFVFKGRWFWRVRHNR-VLDNYPMPIGHFWRGLP---GDISAAYER-QDGRFVFFKGDRYWLFREANLEPGYPQ 452
human MT3-MMP    332 -RPSYPGAKPNICDGNFNTLAILRREMFVFKDQWFWRVRNNR-VMDGYPMQITYFWRGLP---PSIDAVYEN-SDGNFVFFKGNKYWVFKDTTLQPGYPH 425
human MT4-MMP(2) 330 --------VPHRCSTHFDAVAQIRGEAFFFKGKYFWRLTRDRHLVSLQPAQMHRFWRGLPLHLDSVDAVYERTSDHKIVFFKGDRYWVFKDNNVEEGYPR 421
human MT5-MMP    369 -RPSTPGTKPNICDGNFNTVALFRGEMFVFKDRWFWRLRNNR-VQEGYPMQIEQFWKGLP---ARIDAAYER-ADGRFVFFKGDKYWVFKEVTVEPGYPH 462
mouse MT5-MMP    342 -RPSTPGAKPNICDGNFNTVALFRGEMFVFKDRWFWRLRNNR-VQEGYPMQIEQFWKGLP---ARIDAAYER-ADGRFVFFKGDKYWVFKEVTVEPGYPH 435
                          *. *   * ..*  * * * ** . ***.   . .    *  .  **.***     . . **   *   ***** . *.* .  .. ***.

human MT1-MMP    402 HIKELGRGLPTDKIDAALFWMPNGKTYFFRGNKYYRFNEELRAVDSEYPKNIKVWEGIPESPRGSFMGSDEVFTYFYKGNKYWKFNNQKLKVEPGYPKSA 501
human MT2-MMP    453 PLTSYGLGIPYDRIDTAIWWEPTGHTFFFQEDRYWRFNEETQRGDPGYPKPISVWQGIPASPKGAFLSNDAAYTYFYKGTKYWKFDNERLRMEPGYPKSI 552
human MT3-MMP    426 DLITLGSGIPPHGIDSAIWWEDVGKTYFFKGDRYWRYSEEMKTMDPGYPKPITVWKGIPESPQGAFVHKENGFTYFYKGKEYWKFNNQILKVEPGYPRSI 525
human MT4-MMP(2) 422 PVSDFS--LPPGGIDAAFSWAHNDRTYFFKDQLYWRYDDHTRHMDPGYPAQSPLWRGVPSTLDDAMRWSDG-ASYFFRGQEYWKVLDGELEVAPGYPQST 518
human MT5-MMP    463 SLGELGSCLPREGIDTALRWEPVGKTYFFKGERYWRYSEERRATDPGYPKPITVWKGIPQAPQGAFISKEGYYTYFYKGRDYWKFDNQKLSVEPGYPRNI 562
mouse MT5-MMP    436 SLGELGSCLPREGIDTALRWEPVGKTYFFKGERYWCYSEERRATDPGYPKPITVWKGIPQAPQGAFISKEGYYTYFYKGRDYWKFDNQKLSVEPGYPRNI 535
                        .     .*   **.*  *    .*.**.   *  . . .  * **    .* *.* .   .    .   .**..*  ***     * . ****.

human MT1-MMP    502 LRDWMGCPSGGRPDE-------------GTEEETEVIIIEVDE----------EGGG----------AVSAAAVVLPVLLLLLVLAVGLAVFFFRRH 565
human MT2-MMP    553 LRDFMGCQEHVEPGPRWPDVARPPFNPHGGAEPGADSAEGDVGDGDGDFGAGVNKDGGSRVVVQMEEVARTVNVVMVLVPLLLLLCVLGLTYALVQMQRK 652
human MT3-MMP    526 LKDFMGCDG-PTDRVKEGH----------SPPDDVDIVIKLDNTAS----------------------TVKAIAIVIPCILALCLLVLVYTVFQFKRK 590
human MT4-MMP(2) 519 ARDWLVCGDSQADGSVAAGVDAAE---GPRAPPGQHDQSRSEDGYEVC----------------------SCTSGASSPPGAPGPLVAATMLLLLPP--- 590
human MT5-MMP    563 LRDWMGCNQKEVERRKERR----------LPQDDVDIMVTINDVPG----------------------SVNAVAVVIPCILSLCILVLVYTIFQFKNK 628
mouse MT5-MMP    536 LRDWMGCKQKEVERRKERR----------LPQDDVDIMVTIDDVPG----------------------SVNAVAVVVPCTLSLCLLVLLYTIFQFKNK 601
                      .* . *                                                              .       *      .      .

human MT1-MMP    566 GTPRRLLYCQRSLLDKV 582
human MT2-MMP    653 GAPRVLLYCKRSLQEWV 669
human MT3-MMP    591 GTPRHILYCKRSMQEWV 607
human MT4-MMP(2) 591 LSPGALWTAAQALTL-- 605
human MT5-MMP    629 TGPQPVTYYKRPVQEWV 645
mouse MT5-MMP    602 AGPQPVTYYKRPVQEWV 618
                      * .   . .
```

Fig. 2



Attorney's Docket No.:_____

DECLARATION, POWER OF ATTORNEY AND PETITION

I (We), the undersigned inventor(s), hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I (We) believe that I am (we are) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

DNAS ENCODING NOVEL POLYPEPTIDES

the specification of which

☐ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and amended on _____

■ was filed as PCT international application

Number PCT/JP99/05349

on September 29, 1999

and was amended under PCT Article 19

on _____ (if applicable).

I (We) hereby state that I (We) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above; that I (We) do not know and do not believe that this invention was ever known or used before my invention or discovery thereof, or patented or described in any printed publication in any country before my invention or discovery thereof, or more than one year prior to this application, or in public use or on sale in the United States for more than one year prior to this application; that this invention or discovery has not been patented or made the subject of an inventor's certificate in any country foreign to the United States on an application filed by me or my legal representatives or assigns more than twelve months before this application.

I (We) acknowledge the duty to disclose information known to be material to

the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

I (We) hereby claim foreign priority benefits under Section 119(a)-(d) of Title 35 United States Code, of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Application No.	Country	Filing date	Priority claimed
276258/1998	Japan	September 29, 1998	■ Yes ☐ No
291505/1998	Japan	September 29, 1998	■ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

I hereby claim the benefit under Section 119(e) of Title 35 United States Code, of any United States application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

I (We) hereby claim the benefit under Section 120 of Title 35 United States Code, of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Section 112 of Title 35 United States Code, I (We) acknowledge the duty to disclose material information as defined in Section 1.56(a) of Title 37 Code of Federal Regulations, which occurred between the filing date of the prior application and national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (pending, patented, abandoned)

And I (We) hereby appoint: Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., Registration No. 22,540; Douglas B. Henderson, Registration No. 20,291; Ford F. Farabow, Jr., Registration No. 20,630; Arthur S. Garrett, Registration No. 20,338; Donald R. Dunner, Registration No. 19,073; Brian G. Brunsvold, Registration No. 22,593; Tipton D. Jennings, IV, Registration No. 20,645; Jerry D. Voight, Registration No. 23,020; Laurence R. Hefter, Registration No. 20,827; Kenneth E. Payne, Registration No. 23,098; Herbert H. Mintz, Registration No. 26,691; C. Larry O'Rourke, Registration No. 26,014; Albert J. Santorelli, Registration No. 22,610; Michael C. Elmer, Registration No. 25,857; Richard H. Smith, Registration No. 20,609; Stephen L. Peterson, Registration No. 26,325; John M. Romary, Registration No. 26,331; Bruce C. Zotter, Registration No. 27,680; Dennis P. O'Reilley, Registration No. 27,932; Allen M. Sokal, Registration No. 26,695; Robert D. Bajefsky, Registration No. 25,387; Richard L. Stroup, Registration No. 28,478; David W. Hill, Registration No. 28,220; Thomas L. Irving, Registration No. 28,619; Charles E. Lipsey, Registration No. 28,165; Thomas W. Winland, Registration No. 27,605; Basil J. Lewris, Registration No. 28,818; Martin I. Fuchs, Registration No. 28,508; E. Robert Yoches, Registration No. 30,120; Barry W. Graham, Registration No. 29,924; Susan Haberman Griffen, Registration No. 30,907; Richard B. Racine, Registration No. 30,415; Thomas H. Jenkins, Registration No. 30,857; Robert E. Converse, Jr., Registration No. 27,432; Clair X. Mullen, Jr., Registration No. 20,348; Christopher P. Foley, Registration No. 31,354; John C. Paul, Registration No. 30,413; David M. Kelly, Registration No. 30,953; Kenneth J. Meyers, Registration No. 25,146; Carol P. Einaudi, Registration No. 32,220; Walter Y. Boyd, Jr., Registration No. 31,738; Steven M. Anzalone, Registration No. 32,095; Jean B. Fordis, Registration No. 32,984; Barbara C. McCurdy, Registration No. 32,120; James K. Hammond, Registration No. 31,964; Richard V. Burgujian, Registration No. 31,744; J. Michael Jakes, Registration No. 32,824; Thomas W. Banks, Registration No. 32,719; M. Paul Barker, Registration No. 32,013; Bryan C. Diner, Registration No. 32,409; Christopher P. Isaac, Registration No. 32,616; Andrew C. Sonu, Registration No. 33,457; and Dirk D. Thomas, Registration No. 32,600.

I(We) hereby request that all correspondence regarding this application be sent to the firm of FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P. whose Post office address is: 1300 I Street, N.W., WASHINGTON, D.C. 20005 U.S.A.

I (We) declare further that all statements made herein of my (our) knowledge are true and that all statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment,

or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Motoharu SEIKI

NAME OF FIRST SOLE INVENTOR

Signature of Inventor

March 14, 2001

Date

Residence: Tokyo, Japan JPX

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Koyamadai-jutaku 5-203, 2-5,

Koyamadai, Shinagawa-ku,

Tokyo 142-0061 Japan

SEQUENCE LISTING

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Ser Leu Gly Val Glu Trp Leu Ser Arg Phe Gly Tyr Leu Pro Pro Ala
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Asp Glu Ala Thr Leu Ala Leu Met Lys Thr Pro Arg Cys Ser Leu Pro
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Asp Leu Pro Pro Gly Ala Gln Ser Arg Arg Lys Arg Gln Thr Pro Pro
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Ala Phe Phe Pro Gly Asp His His Thr Ala Gly Asp Thr His Phe Asp
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His Val Ala Ala Pro Ser Ser Ile Met Gln Pro Tyr Tyr Gln Gly Pro
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Phe Lys Gly Lys Tyr Phe Trp Arg Leu Thr Arg Asp Arg His Leu Val
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Ser Leu Gln Pro Ala Gln Met His Arg Phe Trp Arg Gly Leu Pro Leu
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His Leu Asp Ser Val Asp Ala Val Tyr Glu Arg Thr Ser Asp His Lys
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Ser Gly Ala Gln Asp Gly Leu Ala Val Cys Ser Cys Thr Ser Asp Ala
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Thr His Phe Asp Asp Asp Glu Ala Trp Thr Phe Arg Ser Ser Asp Ala
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His Gly Met Asp Leu Phe Ala Val Ala Val His Glu Phe Gly His Ala
245 250 255

Ile Gly Leu Ser His Val Ala Ala Ala His Ser Ile Met Arg Pro Tyr
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275 280 285

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Thr His Phe Asp Ala Val Ala Gln Ile Arg Gly Glu Ala Phe Phe Phe
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Lys Gly Lys Tyr Phe Trp Arg Leu Thr Arg Asp Arg His Leu Val Ser
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Gly Ile Asp Ala Ala Phe Ser Trp Ala His Asn Asp Arg Thr Tyr Phe
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Phe Gly Tyr Leu Pro Pro Ala Asp Pro Ala Ser Gly Gln Leu Gln Thr
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Thr Pro Arg Cys Ser Leu Pro Asp Leu Pro Pro Gly Ala Gln Ser Arg
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Ile Asp Phe Ser Lys Ala Asp His Asn Asp Gly Tyr Pro Phe Asp Gly
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Ala Gly Asp Thr His Phe Asp Asp Asp Glu Pro Trp Thr Phe Arg Ser
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Ser Asp Ala His Gly Met Asp Leu Phe Ala Val Ala Val His Glu Phe
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Asn Asp Gly Tyr Pro Phe Asp Gly Pro Gly Gly Thr Val Ala His Ala
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ttc ttc ccc ggc cac cac cac acc gcc ggg gac acc cac ttt gac gat 786
Phe Phe Pro Gly His His His Thr Ala Gly Asp Thr His Phe Asp Asp
215 220 225

gac gag gcc tgg acc ttc cgc tcc tcg gat gcc cac ggg atg gac ctg 834

Asp Glu Ala Trp Thr Phe Arg Ser Ser Asp Ala His Gly Met Asp Leu
230 235 240 245

ttt gca gtg gct gtc cac gag ttt ggc cac gcc att ggg tta agc cat 882
Phe Ala Val Ala Val His Glu Phe Gly His Ala Ile Gly Leu Ser His
250 255 260

gtg gcc gct gca cac tcc atc atg cgg ccg tac tac cag ggc ccg gtg 930
Val Ala Ala Ala His Ser Ile Met Arg Pro Tyr Tyr Gln Gly Pro Val
265 270 275

ggt gac ccg ctg cgc tac ggg ctc ccc tac gag gac aag gtg cgc gtc 978
Gly Asp Pro Leu Arg Tyr Gly Leu Pro Tyr Glu Asp Lys Val Arg Val
280 285 290

tgg cag ctg tac ggt gtg cgg gag tct gtg tct ccc acg gcg cag ccc 1026
Trp Gln Leu Tyr Gly Val Arg Glu Ser Val Ser Pro Thr Ala Gln Pro
295 300 305

gag gag cct ccc ctg ctg ccg gag ccc cca gac aac cgg tcc agc gcc 1074
Glu Glu Pro Pro Leu Leu Pro Glu Pro Pro Asp Asn Arg Ser Ser Ala
310 315 320 325

ccg ccc agg aag gac gtg ccc cac aga tgc agc act cac ttt gac gcg 1122
Pro Pro Arg Lys Asp Val Pro His Arg Cys Ser Thr His Phe Asp Ala
330 335 340

gtg gcc cag atc cgg ggt gaa gct ttc ttc ttc aaa ggc aag tac ttc 1170
Val Ala Gln Ile Arg Gly Glu Ala Phe Phe Phe Lys Gly Lys Tyr Phe

345 350 355

tgg cgg ctg acg cgg gac cgg cac ctg gtg tcc ctg cag ccg gca cag 1218
Trp Arg Leu Thr Arg Asp Arg His Leu Val Ser Leu Gln Pro Ala Gln
360 365 370

atg cac cgc ttc tgg cgg ggc ctg ccg ctg cac ctg gac agc gtg gac 1266
Met His Arg Phe Trp Arg Gly Leu Pro Leu His Leu Asp Ser Val Asp
375 380 385

gcc gtg tac gag cgc acc agc gac cac aag atc gtc ttc ttt aaa gga 1314
Ala Val Tyr Glu Arg Thr Ser Asp His Lys Ile Val Phe Phe Lys Gly
390 395 400 405

gac agg tac tgg gtg ttc aag gac aat aac gta gag gaa gga tac ccg 1362
Asp Arg Tyr Trp Val Phe Lys Asp Asn Asn Val Glu Glu Gly Tyr Pro
410 415 420

cgc ccc gtc tcc gac ttc agc ctc ccg cct ggc ggc atc gac gct gcc 1410
Arg Pro Val Ser Asp Phe Ser Leu Pro Pro Gly Gly Ile Asp Ala Ala
425 430 435

ttc tcc tgg gcc cac aat gac agg act tat ttc ttt aag gac cag ctg 1458
Phe Ser Trp Ala His Asn Asp Arg Thr Tyr Phe Phe Lys Asp Gln Leu
440 445 450

tac tgg cgc tac gat gac cac acg agg cac atg gac ccc ggc tac ccc 1506
Tyr Trp Arg Tyr Asp Asp His Thr Arg His Met Asp Pro Gly Tyr Pro
455 460 465

gcc cag agc ccc ctg tgg agg ggt gtc ccc agc acg ctg gac gac gcc 1554
Ala Gln Ser Pro Leu Trp Arg Gly Val Pro Ser Thr Leu Asp Asp Ala
470 475 480 485

atg cgc tgg tcc gac ggt gcc tcc tac ttc ttc cgt ggc cag gag tac 1602
Met Arg Trp Ser Asp Gly Ala Ser Tyr Phe Phe Arg Gly Gln Glu Tyr
490 495 500

tgg aaa gtg ctg gat ggc gag ctg gag gtg gca ccc ggg tac cca cag 1650
Trp Lys Val Leu Asp Gly Glu Leu Glu Val Ala Pro Gly Tyr Pro Gln
505 510 515

tcc acg gcc cgg gac tgg ctg gtg tgt gga gac tca cag gcc gat gga 1698
Ser Thr Ala Arg Asp Trp Leu Val Cys Gly Asp Ser Gln Ala Asp Gly
520 525 530

tct gtg gct gcg ggc gtg gac gcg gca gag ggg ccc cgc gcc cct cca 1746
Ser Val Ala Ala Gly Val Asp Ala Ala Glu Gly Pro Arg Ala Pro Pro
535 540 545

gga caa cat gac cag agc cgc tcg gag gac ggt tac gag gtc tgc tca 1794
Gly Gln His Asp Gln Ser Arg Ser Glu Asp Gly Tyr Glu Val Cys Ser
550 555 560 565

tgc acc tct ggg gca tcc tct ccc ccg ggg gcc cca ggc cca ctg gtg 1842
Cys Thr Ser Gly Ala Ser Ser Pro Pro Gly Ala Pro Gly Pro Leu Val
570 575 580

gct gcc acc atg ctg ctg ctg ctg ccg cca ctg tca cca ggc gcc ctg 1890
Ala Ala Thr Met Leu Leu Leu Leu Pro Pro Leu Ser Pro Gly Ala Leu
585 590 595

tgg aca gcg gcc cag gcc ctg acg cta tgacacacag cgcgagccca 1937
Trp Thr Ala Ala Gln Ala Leu Thr Leu
600 605

tgagaggaca gaggcggtgg gacagcctgg ccacagaggg caaggactgt gccggagtcc 1997

ctgggggagg tgctggcgcg ggatgaggac gggccaccct ggcaccggaa ggccagcaga 2057

gggcacggcc cgccagggct gggcaggctc aggtggcaag gacggagctg tcccctagtg 2117

agggactgtg ttgactgacg agccgagggg tggccgctcc agaagggtgc ccagtcaggc 2177

cgcaccgccg ccagcctcct ccggccctgg agggagcatc tcgggctggg ggcccacccc 2237

tctctgtgcc ggcgccacca accccaccca cactgctgcc tggtgctccc gccggcccac 2297

agggcctccg tccccaggtc cccagtgggg cagccctccc cacagacgag ccccccacat 2357

ggtgccgcgg cacgtccccc ctgtgacgcg ttccagacca acatgacctc tccctgcttt 2417

gtaaaaaaaa aaaaaaaaaa a 2438

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<211> 618

<212> PRT

<213> Mouse

<400> 5

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Leu Cys Cys Leu Ala Ala Ala Ala Gly Ala Gly Lys Pro Ala Gly Ala
35 40 45

Asp Ala Pro Phe Ala Gly Gln Asn Trp Leu Lys Ser Tyr Gly Tyr Leu
50 55 60

Leu Pro Tyr Glu Ser Arg Ala Ser Ala Leu His Ser Gly Lys Ala Leu
65 70 75 80

Gln Ser Ala Val Ser Thr Met Gln Gln Phe Tyr Gly Ile Pro Val Thr
85 90 95

Gly Val Leu Asp Gln Thr Thr Ile Glu Trp Met Lys Lys Pro Arg Cys
100 105 110

Gly Val Pro Asp His Pro His Leu Ser Arg Arg Arg Arg Arg Asn Lys Arg
115 120 125

Tyr Ala Leu Thr Gly Gln Lys Trp Arg Gln Lys His Ile Thr Tyr Ser

130 135 140

Ile His Asn Tyr Thr Pro Lys Val Gly Glu Leu Asp Thr Arg Lys Ala
145 150 155 160

Ile Arg Gln Ala Phe Asp Val Trp Gln Lys Val Thr Pro Leu Thr Phe
165 170 175

Glu Glu Val Pro Tyr His Glu Ile Lys Ser Asp Arg Lys Glu Ala Asp
180 185 190

Ile Met Ile Phe Phe Ala Ser Gly Phe His Gly Asp Ser Ser Pro Phe
195 200 205

Asp Gly Glu Gly Gly Phe Leu Ala His Ala Tyr Phe Pro Gly Pro Gly
210 215 220

Ile Gly Gly Asp Thr His Phe Asp Ser Asp Glu Pro Trp Thr Leu Gly
225 230 235 240

Asn Ala Asn His Asp Gly Asn Asp Leu Phe Leu Val Ala Val His Glu
245 250 255

Leu Gly His Ala Leu Gly Leu Glu His Ser Asn Asp Pro Ser Ala Ile
260 265 270

Met Ala Pro Phe Tyr Gln Tyr Met Glu Thr His Asn Phe Lys Leu Pro
275 280 285

Gln Asp Asp Leu Gln Gly Ile Gln Lys Ile Tyr Gly Pro Pro Ala Glu
290 295 300

Pro Leu Glu Pro Thr Arg Pro Leu His Thr Leu Pro Val Arg Arg Ile
305 310 315 320

His Ser Pro Ser Glu Arg Lys His Glu Arg His Pro Arg Pro Pro Arg
325 330 335

Pro Pro Leu Gly Asp Arg Pro Ser Thr Pro Gly Ala Lys Pro Asn Ile
340 345 350

Cys Asp Gly Asn Phe Asn Thr Val Ala Leu Phe Arg Gly Glu Met Phe
355 360 365

Val Phe Lys Asp Arg Trp Phe Trp Arg Leu Arg Asn Asn Arg Val Gln
370 375 380

Glu Gly Tyr Pro Met Gln Ile Glu Gln Phe Trp Lys Gly Leu Pro Ala
385 390 395 400

Arg Ile Asp Ala Ala Tyr Glu Arg Ala Asp Gly Arg Phe Val Phe Phe
405 410 415

Lys Gly Asp Lys Tyr Trp Val Phe Lys Glu Val Thr Val Glu Pro Gly
420 425 430

Tyr Pro His Ser Leu Gly Glu Leu Gly Ser Cys Leu Pro Arg Glu Gly
435 440 445

Ile Asp Thr Ala Leu Arg Trp Glu Pro Val Gly Lys Thr Tyr Phe Phe
450 455 460

Lys Gly Glu Arg Tyr Trp Arg Tyr Ser Glu Glu Arg Arg Ala Thr Asp
465 470 475 480

Pro Gly Tyr Pro Lys Pro Ile Thr Val Trp Lys Gly Ile Pro Gln Ala
485 490 495

Pro Gln Gly Ala Phe Ile Ser Lys Glu Gly Tyr Tyr Thr Tyr Phe Tyr
500 505 510

Lys Gly Arg Asp Tyr Trp Lys Phe Asp Asn Gln Lys Leu Ser Val Glu
515 520 525

Pro Gly Tyr Pro Arg Asn Ile Leu Arg Asp Trp Met Gly Cys Lys Gln
530 535 540

Lys Glu Val Glu Arg Arg Lys Glu Arg Arg Leu Pro Gln Asp Asp Val
545 550 555 560

Asp Ile Met Val Thr Ile Asp Asp Val Pro Gly Ser Val Asn Ala Val
565 570 575

Ala Val Val Val Pro Cys Thr Leu Ser Leu Cys Leu Leu Val Leu Leu
580 585 590

Tyr Thr Ile Phe Gln Phe Lys Asn Lys Ala Gly Pro Gln Pro Val Thr

595 600 605

Tyr Tyr Lys Arg Pro Val Gln Glu Trp Val
610 615

<210> 6

<211> 645

<212> PRT

<213> Homo sapiens

<400> 6

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Pro Pro Pro Pro Gly Gln Ala Pro Arg Trp Ser Arg Trp Arg Val Pro
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Gly Arg Leu Leu Leu Leu Leu Leu Pro Ala Leu Cys Cys Leu Pro Gly
35 40 45

Ala Ala Arg Ala Ala Ala Ala Ala Ala Ala Gly Ala Gly Asn Arg Ala Ala
50 55 60

Val Ala Val Ala Val Ala Arg Ala Asp Glu Ala Glu Ala Pro Phe Ala
65 70 75 80

Gly Gln Asn Trp Leu Lys Ser Tyr Gly Tyr Leu Leu Pro Tyr Asp Ser
85 90 95

Arg Ala Ser Ala Leu His Ser Ala Lys Ala Leu Gln Ser Ala Val Ser
100 105 110

Thr Met Gln Gln Phe Tyr Gly Ile Pro Val Thr Gly Val Leu Asp Gln
115 120 125

Thr Thr Ile Glu Trp Met Lys Lys Pro Arg Cys Gly Val Pro Asp His
130 135 140

Pro His Leu Ser Arg Arg Arg Arg Asn Lys Arg Tyr Ala Leu Thr Gly
145 150 155 160

Gln Lys Trp Arg Gln Lys His Ile Thr Tyr Ser Ile His Asn Tyr Thr
165 170 175

Pro Lys Val Gly Glu Leu Asp Thr Arg Lys Ala Ile Arg Gln Ala Phe
180 185 190

Asp Val Trp Gln Lys Val Thr Pro Leu Thr Phe Glu Glu Val Pro Tyr
195 200 205

His Glu Ile Lys Ser Asp Arg Lys Glu Ala Asp Ile Met Ile Phe Phe
210 215 220

Ala Ser Gly Phe His Gly Asp Ser Ser Pro Phe Asp Gly Glu Gly Gly
225 230 235 240

Phe Leu Ala His Ala Tyr Phe Pro Gly Pro Gly Ile Gly Gly Asp Thr
245 250 255

His Phe Asp Ser Asp Glu Pro Trp Thr Leu Gly Asn Ala Asn His Asp
260 265 270

Gly Asn Asp Leu Phe Leu Val Ala Val His Glu Leu Gly His Ala Leu
275 280 285

Gly Leu Glu His Ser Ser Asp Pro Ser Ala Ile Met Ala Pro Phe Tyr
290 295 300

Gln Tyr Met Glu Thr His Asn Phe Lys Leu Pro Gln Asp Asp Leu Gln
305 310 315 320

Gly Ile Gln Lys Ile Tyr Gly Pro Pro Ala Glu Pro Leu Glu Pro Thr
325 330 335

Arg Pro Leu Pro Thr Leu Pro Val Arg Arg Ile His Ser Pro Ser Glu
340 345 350

Arg Lys His Glu Arg Gln Pro Arg Pro Pro Arg Pro Pro Leu Gly Asp
355 360 365

Arg Pro Ser Thr Pro Gly Thr Lys Pro Asn Ile Cys Asp Gly Asn Phe
370 375 380

Asn Thr Val Ala Leu Phe Arg Gly Glu Met Phe Val Phe Lys Asp Arg
385 390 395 400

Trp Phe Trp Arg Leu Arg Asn Asn Arg Val Gln Glu Gly Tyr Pro Met

405 410 415

Gln Ile Glu Gln Phe Trp Lys Gly Leu Pro Ala Arg Ile Asp Ala Ala
420 425 430

Tyr Glu Arg Ala Asp Gly Arg Phe Val Phe Phe Lys Gly Asp Lys Tyr
435 440 445

Trp Val Phe Lys Glu Val Thr Val Glu Pro Gly Tyr Pro His Ser Leu
450 455 460

Gly Glu Leu Gly Ser Cys Leu Pro Arg Glu Gly Ile Asp Thr Ala Leu
465 470 475 480

Arg Trp Glu Pro Val Gly Lys Thr Tyr Phe Phe Lys Gly Glu Arg Tyr
485 490 495

Trp Arg Tyr Ser Glu Glu Arg Arg Ala Thr Asp Pro Gly Tyr Pro Lys
500 505 510

Pro Ile Thr Val Trp Lys Gly Ile Pro Gln Ala Pro Gln Gly Ala Phe
515 520 525

Ile Ser Lys Glu Gly Tyr Tyr Thr Tyr Phe Tyr Lys Gly Arg Asp Tyr
530 535 540

Trp Lys Phe Asp Asn Gln Lys Leu Ser Val Glu Pro Gly Tyr Pro Arg
545 550 555 560

Asn Ile Leu Arg Asp Trp Met Gly Cys Asn Gln Lys Glu Val Glu Arg
565 570 575

Arg Lys Glu Arg Arg Leu Pro Gln Asp Asp Val Asp Ile Met Val Thr
580 585 590

Ile Asn Asp Val Pro Gly Ser Val Asn Ala Val Ala Val Val Ile Pro
595 600 605

Cys Ile Leu Ser Leu Cys Ile Leu Val Leu Val Tyr Thr Ile Phe Gln
610 615 620

Phe Lys Asn Lys Thr Gly Pro Gln Pro Val Thr Tyr Tyr Lys Arg Pro
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Val Gln Glu Trp Val
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<211> 4263

<212> DNA

<213> Mouse

<220>

<221> CDS

<222> (75)..(1928)

<400> 7

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Met Pro Arg Ser Arg Gly Gly Arg Ala Ala Pro Gly
1 5 10

cag gcc tcg cgc tgg agc ggc tgg cgg gcc ccg ggg cgg ctg ctg ccg 158
Gln Ala Ser Arg Trp Ser Gly Trp Arg Ala Pro Gly Arg Leu Leu Pro
15 20 25

ctg ctg ccc gcg ctc tgc tgc ctc gcg gcg gcg gcg ggg gcc ggg aag 206
Leu Leu Pro Ala Leu Cys Cys Leu Ala Ala Ala Ala Gly Ala Gly Lys
30 35 40

ccg gcc ggg gcg gac gcg ccc ttc gct ggg cag aac tgg tta aaa tca 254
Pro Ala Gly Ala Asp Ala Pro Phe Ala Gly Gln Asn Trp Leu Lys Ser
45 50 55 60

tat ggc tat ctg ctt ccc tat gag tcg cgg gca tct gcg ttg cat tct 302
Tyr Gly Tyr Leu Leu Pro Tyr Glu Ser Arg Ala Ser Ala Leu His Ser
65 70 75

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Gly Lys Ala Leu Gln Ser Ala Val Ser Thr Met Gln Gln Phe Tyr Gly
80 85 90

atc cca gtc acc ggt gtg ttg gat cag aca aca atc gag tgg atg aag 398
Ile Pro Val Thr Gly Val Leu Asp Gln Thr Thr Ile Glu Trp Met Lys
95 100 105

aaa cct cga tgt ggc gtc cct gat cat ccc cac ttg agc agg agg agg 446
Lys Pro Arg Cys Gly Val Pro Asp His Pro His Leu Ser Arg Arg Arg
110 115 120

aga aat aag cga tat gcc cta act gga cag aag tgg agg cag aaa cac 494
Arg Asn Lys Arg Tyr Ala Leu Thr Gly Gln Lys Trp Arg Gln Lys His
125 130 135 140

atc acc tac agc att cac aat tat acc cca aag gtg ggt gag ctg gac 542
Ile Thr Tyr Ser Ile His Asn Tyr Thr Pro Lys Val Gly Glu Leu Asp
145 150 155

aca cgg aag gct att cgt cag gct ttc gat gtg tgg cag aag gtg act 590
Thr Arg Lys Ala Ile Arg Gln Ala Phe Asp Val Trp Gln Lys Val Thr
160 165 170

cca ctg acc ttt gaa gag gtg cca tac cat gag atc aaa agt gac cgg 638
Pro Leu Thr Phe Glu Glu Val Pro Tyr His Glu Ile Lys Ser Asp Arg
175 180 185

aag gag gca gac atc atg atc ttc ttt gct tct ggt ttc cat ggt gac 686
Lys Glu Ala Asp Ile Met Ile Phe Phe Ala Ser Gly Phe His Gly Asp
190 195 200

agc tcc cca ttt gat ggg gaa ggg gga ttc cta gcc cat gcc tac ttt 734
Ser Ser Pro Phe Asp Gly Glu Gly Gly Phe Leu Ala His Ala Tyr Phe
205 210 215 220

cct ggc cca ggg atc gga gga gac act cac ttt gat tca gat gaa ccc 782

Pro Gly Pro Gly Ile Gly Gly Asp Thr His Phe Asp Ser Asp Glu Pro
225 230 235

tgg acg cta gga aat gcc aac cat gat ggc aat gac ctc ttc ctg gtg 830
Trp Thr Leu Gly Asn Ala Asn His Asp Gly Asn Asp Leu Phe Leu Val
240 245 250

gcc gtg cat gaa ctg ggc cat gca ctg ggc ttg gag cac tct aat gac 878
Ala Val His Glu Leu Gly His Ala Leu Gly Leu Glu His Ser Asn Asp
255 260 265

ccc agt gct atc atg gct ccc ttc tac caa tac atg gag aca cac aac 926
Pro Ser Ala Ile Met Ala Pro Phe Tyr Gln Tyr Met Glu Thr His Asn
270 275 280

ttc aag cta ccg cag gac gat ctc cag ggc atc cag aag att tac gga 974
Phe Lys Leu Pro Gln Asp Asp Leu Gln Gly Ile Gln Lys Ile Tyr Gly
285 290 295 300

ccc cca gct gag cct ctg gag ccc aca agg ccc ctc cat aca ctc ccg 1022
Pro Pro Ala Glu Pro Leu Glu Pro Thr Arg Pro Leu His Thr Leu Pro
305 310 315

gtc cgc agg atc cac tcg ccg tct gag agg aag cac gag cgg cac cca 1070
Val Arg Arg Ile His Ser Pro Ser Glu Arg Lys His Glu Arg His Pro
320 325 330

agg ccc cca cgg ccg ccc ctt ggg gac cgg cca tcc act cca ggt gcc 1118
Arg Pro Pro Arg Pro Pro Leu Gly Asp Arg Pro Ser Thr Pro Gly Ala

335 340 345

aaa ccc aac atc tgc gat ggc aac ttc aac aca gtg gcc ctc ttc cga 1166
Lys Pro Asn Ile Cys Asp Gly Asn Phe Asn Thr Val Ala Leu Phe Arg
350 355 360

ggg gag atg ttt gtg ttc aag gat cgc tgg ttc tgg cgc ctg cgc aat 1214
Gly Glu Met Phe Val Phe Lys Asp Arg Trp Phe Trp Arg Leu Arg Asn
365 370 375 380

aac cgg gtg cag gaa ggc tac ccc atg cag atc gaa cag ttc tgg aag 1262
Asn Arg Val Gln Glu Gly Tyr Pro Met Gln Ile Glu Gln Phe Trp Lys
385 390 395

ggc ctg ccc gcc cgc ata gac gca gcc tat gaa aga gct gac ggg aga 1310
Gly Leu Pro Ala Arg Ile Asp Ala Ala Tyr Glu Arg Ala Asp Gly Arg
400 405 410

ttc gtc ttc ttc aaa gga gac aag tac tgg gtt ttc aaa gaa gtg acg 1358
Phe Val Phe Phe Lys Gly Asp Lys Tyr Trp Val Phe Lys Glu Val Thr
415 420 425

gtg gaa cct ggg tac ccc cac agc ttg ggg gag ctg gga agc tgc ctg 1406
Val Glu Pro Gly Tyr Pro His Ser Leu Gly Glu Leu Gly Ser Cys Leu
430 435 440

ccc cgt gaa gga att gac aca gct ctg cgc tgg gaa cct gtg ggc aaa 1454
Pro Arg Glu Gly Ile Asp Thr Ala Leu Arg Trp Glu Pro Val Gly Lys
445 450 455 460

acc tac ttc ttc aaa ggc gaa cgg tac tgg cgc tac agc gag gag cgg 1502
Thr Tyr Phe Phe Lys Gly Glu Arg Tyr Trp Arg Tyr Ser Glu Glu Arg
465 470 475

cga gcc aca gac cct ggc tac ccc aag ccc atc acc gtg tgg aag ggc 1550
Arg Ala Thr Asp Pro Gly Tyr Pro Lys Pro Ile Thr Val Trp Lys Gly
480 485 490

atc ccg cag gct ccg caa ggg gcc ttc atc agc aag gaa gga tat tac 1598
Ile Pro Gln Ala Pro Gln Gly Ala Phe Ile Ser Lys Glu Gly Tyr Tyr
495 500 505

acc tac ttc tac aaa ggc cgg gac tac tgg aag ttt gac aac cag aaa 1646
Thr Tyr Phe Tyr Lys Gly Arg Asp Tyr Trp Lys Phe Asp Asn Gln Lys
510 515 520

ctg agc gtg gag cca ggc tac cca cgc aac atc ctg cgt gac tgg atg 1694
Leu Ser Val Glu Pro Gly Tyr Pro Arg Asn Ile Leu Arg Asp Trp Met
525 530 535 540

ggc tgc aag cag aag gag gta gag cgg cgt aag gag cgg agg ctg ccc 1742
Gly Cys Lys Gln Lys Glu Val Glu Arg Arg Lys Glu Arg Arg Leu Pro
545 550 555

cag gat gat gtg gac atc atg gtg acc atc gat gac gtg cca ggc tct 1790
Gln Asp Asp Val Asp Ile Met Val Thr Ile Asp Asp Val Pro Gly Ser
560 565 570

gtg aac gct gtg gct gtg gtt gtc ccc tgc aca ctg tcc ctc tgc ctc 1838
Val Asn Ala Val Ala Val Val Val Pro Cys Thr Leu Ser Leu Cys Leu
575 580 585

ctg gtg ctg ctc tac act atc ttc caa ttc aag aac aag gcg ggt cct 1886
Leu Val Leu Leu Tyr Thr Ile Phe Gln Phe Lys Asn Lys Ala Gly Pro
590 595 600

cag ccc gtc acc tac tat aag cgg ccg gtc cag gag tgg gta 1928
Gln Pro Val Thr Tyr Tyr Lys Arg Pro Val Gln Glu Trp Val
605 610 615

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ggctatgccc aggttgggta gctggcaccc agctgccagc cttctgtcct gggcagacct 2168

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cccctgaggt cattgcatcc tgtggtgtct gcaagatacc acagctccag tcctggctgg 2288

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caaactacct ttttgttgtt tgttttaacc tgaggccctt cttcacatct gacagttcct 3248

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gacagagact ctcgatgccc tgggagttgt tgagtaaaat ctcttgtccc agaagcacct 3488

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gttttatact ttgcaaagca ctttattagc tcacagctgt ccactcacat gaaactcctg 3668

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gaggcttcca atcttggatt cttctgcctg cggtcatctg tttgtccatc agcccaggtc 4088

agagcagtca gaggggcaaa gtactggagc ccccagagct cagcttcccc tcggcctggg 4148

tgacatcaca gcatctcagt gtcggtcaca ttttaaactg atcagccttt gtacaatgtt 4208

ttttaaatca tttctaaata aaacagaaat acagtgttaa aaaaaaaaaa aaaaa 4263

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<211> 2620

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)..(1935)

<400> 8

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1 5 10 15

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Pro Pro Pro Pro Gly Gln Ala Pro Arg Trp Ser Arg Trp Arg Val Pro
20 25 30

ggg cgg ctg ctg ctg ctg ctg ctg ccc gcg ctc tgc tgc ctc ccg ggc 144
Gly Arg Leu Leu Leu Leu Leu Leu Pro Ala Leu Cys Cys Leu Pro Gly
35 40 45

gcc gcg cgg gcg gcg gcg gcg gcg gcg ggg gca ggg aac cgg gca gcg 192
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Glu Pro Leu Ala Asp Ala Glu Asp Val Gly Pro Gly Pro Gln Gly Arg
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Ser Gly Ala Gln Asp Gly Leu Ala Val Cys Ser Cys Thr Ser Asp Ala
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Ala Glu Asp Leu Ser Leu Gly Val Glu Trp Leu Ser Arg Phe Gly Tyr
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Leu Pro Pro Ala Asp Pro Thr Thr Gly Gln Leu Gln Thr Gln Glu Glu
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Leu Ser Lys Ala Ile Thr Ala Met Gln Gln Phe Gly Gly Leu Glu Ala
85 90 95

Thr Gly Ile Leu Asp Glu Ala Thr Leu Ala Leu Met Lys Thr Pro Arg
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Cys Ser Leu Pro Asp Leu Pro Val Leu Thr Gln Ala Arg Arg Arg Arg
115 120 125

Gln Ala Pro Ala Pro Thr Lys Trp Asn Lys Arg Asn Leu Ser Trp Arg
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Val Arg Thr Phe Pro Arg Asp Ser Pro Leu Gly His Asp Thr Val Arg
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Ala Leu Met Tyr Tyr Ala Leu Lys Val Trp Ser Asp Ile Ala Pro Leu
165 170 175

Asn Phe His Glu Val Ala Gly Ser Thr Ala Asp Ile Gln Ile Asp Phe
180 185 190

Ser Lys Ala Asp His Asn Asp Gly Tyr Pro Phe Asp Gly Pro Gly Gly
195 200 205

Thr Val Ala His Ala Phe Phe Pro Gly His His His Thr Ala Gly Asp
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Thr His Phe Asp Asp Asp Glu Ala Trp Thr Phe Arg Ser Ser Asp Ala
225 230 235 240

His Gly Met Asp Leu Phe Ala Val Ala Val His Glu Phe Gly His Ala
245 250 255

Ile Gly Leu Ser His Val Ala Ala Ala His Ser Ile Met Arg Pro Tyr
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Tyr Gln Gly Pro Val Gly Asp Pro Leu Arg Tyr Gly Leu Pro Tyr Glu
275 280 285

Asp Lys Val Arg Val Trp Gln Leu Tyr Gly Val Arg Glu Ser Val Ser
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Pro Thr Ala Gln Pro Glu Glu Pro Pro Leu Leu Pro Glu Pro Pro Asp
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Asn Arg Ser Ser Ala Pro Pro Arg Lys Asp Val Pro His Arg Cys Ser
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Thr His Phe Asp Ala Val Ala Gln Ile Arg Gly Glu Ala Phe Phe Phe

340 345 350

Lys Gly Lys Tyr Phe Trp Arg Leu Thr Arg Asp Arg His Leu Val Ser
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Leu Gln Pro Ala Gln Met His Arg Phe Trp Arg Gly Leu Pro Leu His
370 375 380

Leu Asp Ser Val Asp Ala Val Tyr Glu Arg Thr Ser Asp His Lys Ile
385 390 395 400

Val Phe Phe Lys Gly Asp Arg Tyr Trp Val Phe Lys Asp Asn Asn Val
405 410 415

Glu Glu Gly Tyr Pro Arg Pro Val Ser Asp Phe Ser Leu Pro Pro Gly
420 425 430

Gly Ile Asp Ala Ala Phe Ser Trp Ala His Asn Asp Arg Thr Tyr Phe
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Phe Lys Asp Gln Leu Tyr Trp Arg Tyr Asp Asp His Thr Arg His Met
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Asp Pro Gly Tyr Pro Ala Gln Ser Pro Leu Trp Arg Gly Val Pro Ser
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Thr Leu Asp Asp Ala Met Arg Trp Ser Asp Gly Ala Ser Tyr Phe Phe
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Arg Gly Gln Glu Tyr Trp Lys Val Leu Asp Gly Glu Leu Glu Val Ala
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Pro Gly Tyr Pro Gln Ser Thr Ala Arg Asp Trp Leu Val Cys Gly Asp
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Ser Gln Ala Asp Gly Ser Val Ala Ala Gly Val Asp Ala Ala Glu Gly
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Pro Arg Ala Pro Pro Gly Gln His Asp Gln Ser Arg Ser Glu Asp Gly
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Tyr Glu Val Cys Ser Cys Thr Ser Gly Ala Ser Ser Pro Pro Gly Ala
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Met Gly Arg Arg Pro Arg Gly Pro Gly
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Ser Pro Arg Gly Pro Gly Pro Pro Arg Pro Gly Pro Gly Leu Pro Pro
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Leu Leu Leu Val Leu Ala Leu Ala Ala His Gly Gly Cys Ala Ala Pro
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Ala Pro Arg Ala Glu Asp Leu Ser Leu Gly Val Glu Trp Leu Ser Arg
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Phe Gly Tyr Leu Pro Pro Ala Asp Pro Ala Ser Gly Gln Leu Gln Thr
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Gln Glu Glu Leu Ser Lys Ala Ile Thr Ala Met Gln Gln Phe Gly Gly
75 80 85

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Leu Glu Thr Thr Gly Ile Leu Asp Glu Ala Thr Leu Ala Leu Met Lys
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Thr Pro Arg Cys Ser Leu Pro Asp Leu Pro Pro Gly Ala Gln Ser Arg
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Arg Lys Arg Gln Thr Pro Pro Pro Thr Lys Trp Ser Lys Arg Asn Leu
125 130 135

tct tgg agg gtc cgg aca ttc cca cgg gac tca ccc ctg ggc cgg gat 544
Ser Trp Arg Val Arg Thr Phe Pro Arg Asp Ser Pro Leu Gly Arg Asp
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act gtg cgt gca ctc atg tac tac gcc ctc aaa gtc tgg agt gac atc 592
Thr Val Arg Ala Leu Met Tyr Tyr Ala Leu Lys Val Trp Ser Asp Ile

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aca ccc ttg aac ttc cac gag gta gcg ggc aac gcg gcg gac atc cag   640
Thr Pro Leu Asn Phe His Glu Val Ala Gly Asn Ala Ala Asp Ile Gln
170                 175                 180                 185

atc gac ttc tcc aag gcc gac cac aat gac ggc tac ccc ttc gat ggc   688
Ile Asp Phe Ser Lys Ala Asp His Asn Asp Gly Tyr Pro Phe Asp Gly
                190                 195                 200

cct ggt ggc acg gtg gcc cac gca ttc ttc cct ggt gac cac cac acg   736
Pro Gly Gly Thr Val Ala His Ala Phe Phe Pro Gly Asp His His Thr
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gca ggg gac acc cac ttt gat gac gat gag cca tgg acc ttc cgt tcc   784
Ala Gly Asp Thr His Phe Asp Asp Asp Glu Pro Trp Thr Phe Arg Ser
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tca gat gcc cac ggg atg gac ctg ttt gca gtg gcc gtc cat gag ttt   832
Ser Asp Ala His Gly Met Asp Leu Phe Ala Val Ala Val His Glu Phe
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ggt cat gcc att ggt ctg agc cat gtt gcc gcc cca agc tcc atc atg   880
Gly His Ala Ile Gly Leu Ser His Val Ala Ala Pro Ser Ser Ile Met
250                 255                 260                 265

caa ccg tac tac cag ggc ccc gtg ggt gac ccc gta cgc tat gga ctt   928
Gln Pro Tyr Tyr Gln Gly Pro Val Gly Asp Pro Val Arg Tyr Gly Leu
                270                 275                 280

ccg tat gag gac agg gtg cgt gtc tgg cag ttg tac ggt gtg cgg gaa   976
Pro Tyr Glu Asp Arg Val Arg Val Trp Gln Leu Tyr Gly Val Arg Glu
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tcc gtg tcc cct act gcc cag ctg gat acc cca gag ccc gag gag cca  1024
Ser Val Ser Pro Thr Ala Gln Leu Asp Thr Pro Glu Pro Glu Glu Pro
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ccc ctc ctg cca gag ccc ccc aac aat cgg tct agc act ccg ccc cag  1072
Pro Leu Leu Pro Glu Pro Pro Asn Asn Arg Ser Ser Thr Pro Pro Gln
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aag gac gtg cct cac agg tgc act gcc cac ttt gat gct gtg gcc cag  1120
Lys Asp Val Pro His Arg Cys Thr Ala His Phe Asp Ala Val Ala Gln
330                 335                 340                 345

att cga ggc gaa gca ttc ttt ttc aaa ggc aag tat ttc tgg agg ctg  1168
Ile Arg Gly Glu Ala Phe Phe Phe Lys Gly Lys Tyr Phe Trp Arg Leu
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acc cgg gac cga cac ttg gtg tcg ctg cag ccg gct caa atg cat cgc  1216
Thr Arg Asp Arg His Leu Val Ser Leu Gln Pro Ala Gln Met His Arg
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ttc tgg cgg ggc ctg ccg ctg cac ctg gac agt gtg gac gcc gtg tat   1264
Phe Trp Arg Gly Leu Pro Leu His Leu Asp Ser Val Asp Ala Val Tyr
        380                 385                 390

gag cgt acc agt gac cac aag att gtc ttc ttc aaa gga gac aga tac   1312
Glu Arg Thr Ser Asp His Lys Ile Val Phe Phe Lys Gly Asp Arg Tyr
    395                 400                 405

tgg gtg ttt aag gac aac aac gta gag gaa ggg tac ccg cga cct gtc   1360
Trp Val Phe Lys Asp Asn Asn Val Glu Glu Gly Tyr Pro Arg Pro Val
410                 415                 420                 425

tcc gac ttc agc ctc ccg cca ggt ggc atc gat gct gtc ttc tcc tgg   1408
Ser Asp Phe Ser Leu Pro Pro Gly Gly Ile Asp Ala Val Phe Ser Trp
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gcc cac aat gac agg act tat ttc ttt aag gac cag ctg tac tgg cgc   1456
Ala His Asn Asp Arg Thr Tyr Phe Phe Lys Asp Gln Leu Tyr Trp Arg
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tat gat gac cac aca cgg cgc atg gac cct ggc tac cct gcc cag gga   1504
Tyr Asp Asp His Thr Arg Arg Met Asp Pro Gly Tyr Pro Ala Gln Gly
        460                 465                 470

ccc ctg tgg aga ggt gtc ccc agc atg ttg gat gat gcc atg cgc tgg   1552
Pro Leu Trp Arg Gly Val Pro Ser Met Leu Asp Asp Ala Met Arg Trp
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tct gat ggt gca tcc tat ttc ttc cga ggc cag gag tac tgg aaa gtg   1600
Ser Asp Gly Ala Ser Tyr Phe Phe Arg Gly Gln Glu Tyr Trp Lys Val
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ctg gat ggc gag ctg gaa gca gcc ccc ggg tac cca cag tct aca gcc   1648
Leu Asp Gly Glu Leu Glu Ala Ala Pro Gly Tyr Pro Gln Ser Thr Ala
                510                 515                 520

cgc gac tgg ctg gta tgc ggt gag ccg ctg gcg gat gcg gag gat gta   1696
Arg Asp Trp Leu Val Cys Gly Glu Pro Leu Ala Asp Ala Glu Asp Val
            525                 530                 535

ggg cct gga ccc cag ggc cgc agt ggg gcc caa gat ggt ctg gca gta   1744
Gly Pro Gly Pro Gln Gly Arg Ser Gly Ala Gln Asp Gly Leu Ala Val
        540                 545                 550

tgt tcc tgc act tca gac gca cac agg ttg gca ctg cca tct ctg ctg   1792
Cys Ser Cys Thr Ser Asp Ala His Arg Leu Ala Leu Pro Ser Leu Leu
    555                 560                 565

ctt ctg act cca ctg ctg tgg ggc ctg tgg acc tca gtc tct gcc aag   1840
Leu Leu Thr Pro Leu Leu Trp Gly Leu Trp Thr Ser Val Ser Ala Lys
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570 575 580 585

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Ala Ser

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Met Arg Arg Arg Ala
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Ala Arg Gly Pro Gly Pro Pro Pro Pro Gly Pro Gly Leu Ser Arg Leu
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ccg ctg ctg ccg ctg ccg ctg ctg ctg ctg ctg gcg ctg ggg acc cgc 210
Pro Leu Leu Pro Leu Pro Leu Leu Leu Leu Leu Ala Leu Gly Thr Arg
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Gly Gly Cys Ala Ala Pro Glu Pro Ala Arg Arg Ala Glu Asp Leu Ser
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Leu Gly Val Glu Trp Leu Ser Arg Phe Gly Tyr Leu Pro Pro Ala Asp
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ccc aca aca ggg cag ctg cag acg caa gag gag ctg tct aag gcc atc 354
Pro Thr Thr Gly Gln Leu Gln Thr Gln Glu Glu Leu Ser Lys Ala Ile
70 75 80 85

aca gcc atg cag cag ttt ggt ggc ctg gag gcc acc ggc atc ctg gac 402
Thr Ala Met Gln Gln Phe Gly Gly Leu Glu Ala Thr Gly Ile Leu Asp
90 95 100

gag gcc acc ctg gcc ctg atg aaa acc cca cgc tgc tcc ctg cca gac 450
Glu Ala Thr Leu Ala Leu Met Lys Thr Pro Arg Cys Ser Leu Pro Asp
105 110 115

ctc cct gtc ctg acc cag gct cgc agg aga cgc cag gct cca gcc ccc 498
Leu Pro Val Leu Thr Gln Ala Arg Arg Arg Arg Gln Ala Pro Ala Pro
120 125 130

acc aag tgg aac aag agg aac ctg tcg tgg agg gtc cgg acg ttc cca 546
Thr Lys Trp Asn Lys Arg Asn Leu Ser Trp Arg Val Arg Thr Phe Pro
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cgg gac tca cca ctg ggg cac gac acg gtg cgt gca ctc atg tac tac 594
Arg Asp Ser Pro Leu Gly His Asp Thr Val Arg Ala Leu Met Tyr Tyr
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Ala Leu Lys Val Trp Ser Asp Ile Ala Pro Leu Asn Phe His Glu Val
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gcg ggc agc acc gcc gac atc cag atc gac ttc tcc aag gcc gac cat 690
Ala Gly Ser Thr Ala Asp Ile Gln Ile Asp Phe Ser Lys Ala Asp His
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Asn Asp Gly Tyr Pro Phe Asp Gly Pro Gly Gly Thr Val Ala His Ala
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Phe Phe Pro Gly His His His Thr Ala Gly Asp Thr His Phe Asp Asp
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gac gag gcc tgg acc ttc cgc tcc tcg gat gcc cac ggg atg gac ctg 834
Asp Glu Ala Trp Thr Phe Arg Ser Ser Asp Ala His Gly Met Asp Leu
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Phe Ala Val Ala Val His Glu Phe Gly His Ala Ile Gly Leu Ser His
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Val Ala Ala Ala His Ser Ile Met Arg Pro Tyr Tyr Gln Gly Pro Val
265 270 275

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Gly Asp Pro Leu Arg Tyr Gly Leu Pro Tyr Glu Asp Lys Val Arg Val
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tgg cag ctg tac ggt gtg cgg gag tct gtg tct ccc acg gcg cag ccc 1026
Trp Gln Leu Tyr Gly Val Arg Glu Ser Val Ser Pro Thr Ala Gln Pro
295 300 305

gag gag cct ccc ctg ctg ccg gag ccc cca gac aac cgg tcc agc gcc 1074
Glu Glu Pro Pro Leu Leu Pro Glu Pro Pro Asp Asn Arg Ser Ser Ala
310 315 320 325

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ccg ccc agg aag gac gtg ccc cac aga tgc agc act cac ttt gac gcg   1122
Pro Pro Arg Lys Asp Val Pro His Arg Cys Ser Thr His Phe Asp Ala
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gtg gcc cag atc cgg ggt gaa gct ttc ttc ttc aaa ggc aag tac ttc   1170
Val Ala Gln Ile Arg Gly Glu Ala Phe Phe Phe Lys Gly Lys Tyr Phe
            345                 350                 355

tgg cgg ctg acg cgg gac cgg cac ctg gtg tcc ctg cag ccg gca cag   1218
Trp Arg Leu Thr Arg Asp Arg His Leu Val Ser Leu Gln Pro Ala Gln
        360                 365                 370

atg cac cgc ttc tgg cgg ggc ctg ccg ctg cac ctg gac agc gtg gac   1266
Met His Arg Phe Trp Arg Gly Leu Pro Leu His Leu Asp Ser Val Asp
    375                 380                 385

gcc gtg tac gag cgc acc agc gac cac aag atc gtc ttc ttt aaa gga   1314
Ala Val Tyr Glu Arg Thr Ser Asp His Lys Ile Val Phe Phe Lys Gly
390                 395                 400                 405

gac agg tac tgg gtg ttc aag gac aat aac gta gag gaa gga tac ccg   1362
Asp Arg Tyr Trp Val Phe Lys Asp Asn Asn Val Glu Glu Gly Tyr Pro
                410                 415                 420

cgc ccc gtc tcc gac ttc agc ctc ccg cct ggc ggc atc gac gct gcc   1410
Arg Pro Val Ser Asp Phe Ser Leu Pro Pro Gly Gly Ile Asp Ala Ala
            425                 430                 435

ttc tcc tgg gcc cac aat gac agg act tat ttc ttt aag gac cag ctg   1458
Phe Ser Trp Ala His Asn Asp Arg Thr Tyr Phe Phe Lys Asp Gln Leu
        440                 445                 450

tac tgg cgc tac gat gac cac acg agg cac atg gac ccc ggc tac ccc   1506
Tyr Trp Arg Tyr Asp Asp His Thr Arg His Met Asp Pro Gly Tyr Pro
    455                 460                 465

gcc cag agc ccc ctg tgg agg ggt gtc ccc agc acg ctg gac gac gcc   1554
Ala Gln Ser Pro Leu Trp Arg Gly Val Pro Ser Thr Leu Asp Asp Ala
470                 475                 480                 485

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Met Arg Trp Ser Asp Gly Ala Ser Tyr Phe Phe Arg Gly Gln Glu Tyr
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tgg aaa gtg ctg gat ggc gag ctg gag gtg gca ccc ggg tac cca cag   1650
Trp Lys Val Leu Asp Gly Glu Leu Glu Val Ala Pro Gly Tyr Pro Gln
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tcc acg gcc cgg gac tgg ctg gtg tgt gga gac tca cag gcc gat gga   1698
Ser Thr Ala Arg Asp Trp Leu Val Cys Gly Asp Ser Gln Ala Asp Gly
        520                 525                 530
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tct gtg gct gcg ggc gtg gac gcg gca gag ggg ccc cgc gcc cct cca   1746
Ser Val Ala Ala Gly Val Asp Ala Ala Glu Gly Pro Arg Ala Pro Pro
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gga caa cat gac cag agc cgc tcg gag gac ggt tac gag gtc tgc tca   1794
Gly Gln His Asp Gln Ser Arg Ser Glu Asp Gly Tyr Glu Val Cys Ser
550                 555                 560                 565

tgc acc tct ggg gca tcc tct ccc ccg ggg gcc cca ggc cca ctg gtg   1842
Cys Thr Ser Gly Ala Ser Ser Pro Pro Gly Ala Pro Gly Pro Leu Val
                570                 575                 580

gct gcc acc atg ctg ctg ctg ctg ccg cca ctg tca cca ggc gcc ctg   1890
Ala Ala Thr Met Leu Leu Leu Leu Pro Pro Leu Ser Pro Gly Ala Leu
            585                 590                 595

tgg aca gcg gcc cag gcc ctg acg cta tgacacacag cgcgagccca         1937
Trp Thr Ala Ala Gln Ala Leu Thr Leu
        600                 605

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Leu Cys Cys Leu Ala Ala Ala Ala Gly Ala Gly Lys Pro Ala Gly Ala
```

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Asp Ala Pro Phe Ala Gly Gln Asn Trp Leu Lys Ser Tyr Gly Tyr Leu
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Leu Pro Tyr Glu Ser Arg Ala Ser Ala Leu His Ser Gly Lys Ala Leu
 65                  70                  75                  80

Gln Ser Ala Val Ser Thr Met Gln Gln Phe Tyr Gly Ile Pro Val Thr
                 85                  90                  95

Gly Val Leu Asp Gln Thr Thr Ile Glu Trp Met Lys Lys Pro Arg Cys
            100                 105                 110

Gly Val Pro Asp His Pro His Leu Ser Arg Arg Arg Arg Asn Lys Arg
        115                 120                 125

Tyr Ala Leu Thr Gly Gln Lys Trp Arg Gln Lys His Ile Thr Tyr Ser
    130                 135                 140

Ile His Asn Tyr Thr Pro Lys Val Gly Glu Leu Asp Thr Arg Lys Ala
145                 150                 155                 160

Ile Arg Gln Ala Phe Asp Val Trp Gln Lys Val Thr Pro Leu Thr Phe
                165                 170                 175

Glu Glu Val Pro Tyr His Glu Ile Lys Ser Asp Arg Lys Glu Ala Asp
            180                 185                 190

Ile Met Ile Phe Phe Ala Ser Gly Phe His Gly Asp Ser Ser Pro Phe
        195                 200                 205

Asp Gly Glu Gly Gly Phe Leu Ala His Ala Tyr Phe Pro Gly Pro Gly
    210                 215                 220

Ile Gly Gly Asp Thr His Phe Asp Ser Asp Glu Pro Trp Thr Leu Gly
225                 230                 235                 240

Asn Ala Asn His Asp Gly Asn Asp Leu Phe Leu Val Ala Val His Glu
                245                 250                 255

Leu Gly His Ala Leu Gly Leu Glu His Ser Asn Asp Pro Ser Ala Ile
            260                 265                 270

Met Ala Pro Phe Tyr Gln Tyr Met Glu Thr His Asn Phe Lys Leu Pro
        275                 280                 285

Gln Asp Asp Leu Gln Gly Ile Gln Lys Ile Tyr Gly Pro Pro Ala Glu
    290                 295                 300

Pro Leu Glu Pro Thr Arg Pro Leu His Thr Leu Pro Val Arg Arg Ile
305                 310                 315                 320
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His Ser Pro Ser Glu Arg Lys His Glu Arg His Pro Arg Pro Pro Arg
                325                 330                 335

Pro Pro Leu Gly Asp Arg Pro Ser Thr Pro Gly Ala Lys Pro Asn Ile
            340                 345                 350

Cys Asp Gly Asn Phe Asn Thr Val Ala Leu Phe Arg Gly Glu Met Phe
        355                 360                 365

Val Phe Lys Asp Arg Trp Phe Trp Arg Leu Arg Asn Asn Arg Val Gln
    370                 375                 380

Glu Gly Tyr Pro Met Gln Ile Glu Gln Phe Trp Lys Gly Leu Pro Ala
385                 390                 395                 400

Arg Ile Asp Ala Ala Tyr Glu Arg Ala Asp Gly Arg Phe Val Phe Phe
                405                 410                 415

Lys Gly Asp Lys Tyr Trp Val Phe Lys Glu Val Thr Val Glu Pro Gly
            420                 425                 430

Tyr Pro His Ser Leu Gly Glu Leu Gly Ser Cys Leu Pro Arg Glu Gly
        435                 440                 445

Ile Asp Thr Ala Leu Arg Trp Glu Pro Val Gly Lys Thr Tyr Phe Phe
    450                 455                 460

Lys Gly Glu Arg Tyr Trp Arg Tyr Ser Glu Glu Arg Arg Ala Thr Asp
465                 470                 475                 480

Pro Gly Tyr Pro Lys Pro Ile Thr Val Trp Lys Gly Ile Pro Gln Ala
                485                 490                 495

Pro Gln Gly Ala Phe Ile Ser Lys Glu Gly Tyr Tyr Thr Tyr Phe Tyr
            500                 505                 510

Lys Gly Arg Asp Tyr Trp Lys Phe Asp Asn Gln Lys Leu Ser Val Glu
        515                 520                 525

Pro Gly Tyr Pro Arg Asn Ile Leu Arg Asp Trp Met Gly Cys Lys Gln
    530                 535                 540

Lys Glu Val Glu Arg Arg Lys Glu Arg Arg Leu Pro Gln Asp Asp Val
545                 550                 555                 560

Asp Ile Met Val Thr Ile Asp Asp Val Pro Gly Ser Val Asn Ala Val
                565                 570                 575

Ala Val Val Val Pro Cys Thr Leu Ser Leu Cys Leu Leu Val Leu Leu
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Tyr Thr Ile Phe Gln Phe Lys Asn Lys Ala Gly Pro Gln Pro Val Thr
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595 600 605

Tyr Tyr Lys Arg Pro Val Gln Glu Trp Val
610 615

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Pro Pro Pro Pro Gly Gln Ala Pro Arg Trp Ser Arg Trp Arg Val Pro
20 25 30

Gly Arg Leu Leu Leu Leu Leu Leu Pro Ala Leu Cys Cys Leu Pro Gly
35 40 45

Ala Ala Arg Ala Ala Ala Ala Ala Ala Gly Ala Gly Asn Arg Ala Ala
50 55 60

Val Ala Val Ala Val Ala Arg Ala Asp Glu Ala Glu Ala Pro Phe Ala
65 70 75 80

Gly Gln Asn Trp Leu Lys Ser Tyr Gly Tyr Leu Leu Pro Tyr Asp Ser
85 90 95

Arg Ala Ser Ala Leu His Ser Ala Lys Ala Leu Gln Ser Ala Val Ser
100 105 110

Thr Met Gln Gln Phe Tyr Gly Ile Pro Val Thr Gly Val Leu Asp Gln
115 120 125

Thr Thr Ile Glu Trp Met Lys Lys Pro Arg Cys Gly Val Pro Asp His
130 135 140

Pro His Leu Ser Arg Arg Arg Arg Asn Lys Arg Tyr Ala Leu Thr Gly
145 150 155 160

Gln Lys Trp Arg Gln Lys His Ile Thr Tyr Ser Ile His Asn Tyr Thr
165 170 175

Pro Lys Val Gly Glu Leu Asp Thr Arg Lys Ala Ile Arg Gln Ala Phe
180 185 190

Asp Val Trp Gln Lys Val Thr Pro Leu Thr Phe Glu Glu Val Pro Tyr
195 200 205

His Glu Ile Lys Ser Asp Arg Lys Glu Ala Asp Ile Met Ile Phe Phe
210 215 220

Ala Ser Gly Phe His Gly Asp Ser Ser Pro Phe Asp Gly Glu Gly Gly
225 230 235 240

Phe Leu Ala His Ala Tyr Phe Pro Gly Pro Gly Ile Gly Gly Asp Thr
245 250 255

His Phe Asp Ser Asp Glu Pro Trp Thr Leu Gly Asn Ala Asn His Asp
260 265 270

Gly Asn Asp Leu Phe Leu Val Ala Val His Glu Leu Gly His Ala Leu
275 280 285

Gly Leu Glu His Ser Ser Asp Pro Ser Ala Ile Met Ala Pro Phe Tyr
290 295 300

Gln Tyr Met Glu Thr His Asn Phe Lys Leu Pro Gln Asp Asp Leu Gln
305 310 315 320

Gly Ile Gln Lys Ile Tyr Gly Pro Pro Ala Glu Pro Leu Glu Pro Thr
325 330 335

Arg Pro Leu Pro Thr Leu Pro Val Arg Arg Ile His Ser Pro Ser Glu
340 345 350

Arg Lys His Glu Arg Gln Pro Arg Pro Pro Arg Pro Pro Leu Gly Asp
355 360 365

Arg Pro Ser Thr Pro Gly Thr Lys Pro Asn Ile Cys Asp Gly Asn Phe
370 375 380

Asn Thr Val Ala Leu Phe Arg Gly Glu Met Phe Val Phe Lys Asp Arg
385 390 395 400

Trp Phe Trp Arg Leu Arg Asn Asn Arg Val Gln Glu Gly Tyr Pro Met
405 410 415

Gln Ile Glu Gln Phe Trp Lys Gly Leu Pro Ala Arg Ile Asp Ala Ala
420 425 430

Tyr Glu Arg Ala Asp Gly Arg Phe Val Phe Phe Lys Gly Asp Lys Tyr
435 440 445

Trp Val Phe Lys Glu Val Thr Val Glu Pro Gly Tyr Pro His Ser Leu
450 455 460

Gly Glu Leu Gly Ser Cys Leu Pro Arg Glu Gly Ile Asp Thr Ala Leu
465 470 475 480

Arg Trp Glu Pro Val Gly Lys Thr Tyr Phe Phe Lys Gly Glu Arg Tyr
485 490 495

Trp Arg Tyr Ser Glu Glu Arg Arg Ala Thr Asp Pro Gly Tyr Pro Lys

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                500                 505                 510

Pro Ile Thr Val Trp Lys Gly Ile Pro Gln Ala Pro Gln Gly Ala Phe
        515                 520                 525

Ile Ser Lys Glu Gly Tyr Tyr Thr Tyr Phe Tyr Lys Gly Arg Asp Tyr
    530                 535                 540

Trp Lys Phe Asp Asn Gln Lys Leu Ser Val Glu Pro Gly Tyr Pro Arg
545                 550                 555                 560

Asn Ile Leu Arg Asp Trp Met Gly Cys Asn Gln Lys Glu Val Glu Arg
                565                 570                 575

Arg Lys Glu Arg Arg Leu Pro Gln Asp Asp Val Asp Ile Met Val Thr
            580                 585                 590

Ile Asn Asp Val Pro Gly Ser Val Asn Ala Val Ala Val Val Ile Pro
        595                 600                 605

Cys Ile Leu Ser Leu Cys Ile Leu Val Leu Val Tyr Thr Ile Phe Gln
    610                 615                 620

Phe Lys Asn Lys Thr Gly Pro Gln Pro Val Thr Tyr Tyr Lys Arg Pro
625                 630                 635                 640

Val Gln Glu Trp Val
                645
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ccccccgccgc cggg atg ccg agg agc cgg ggc ggc cgc gct gcg ccg ggc   110
                Met Pro Arg Ser Arg Gly Gly Arg Ala Ala Pro Gly
                  1               5                   10

cag gcc tcg cgc tgg agc ggc tgg cgg gcc ccg ggg cgg ctg ctg ccg   158
Gln Ala Ser Arg Trp Ser Gly Trp Arg Ala Pro Gly Arg Leu Leu Pro
          15                  20                  25

ctg ctg ccc gcg ctc tgc tgc ctc gcg gcg gcg gcg ggg gcc ggg aag   206
Leu Leu Pro Ala Leu Cys Cys Leu Ala Ala Ala Ala Gly Ala Gly Lys
     30                  35                  40
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ccg gcc ggg gcg gac gcg ccc ttc gct ggg cag aac tgg tta aaa tca   254
Pro Ala Gly Ala Asp Ala Pro Phe Ala Gly Gln Asn Trp Leu Lys Ser
 45                  50                  55                  60

tat ggc tat ctg ctt ccc tat gag tcg cgg gca tct gcg ttg cat tct   302
Tyr Gly Tyr Leu Leu Pro Tyr Glu Ser Arg Ala Ser Ala Leu His Ser
                 65                  70                  75

ggg aag gcc ttg cag tcc gcg gtc tcc act atg cag cag ttt tac ggg   350
Gly Lys Ala Leu Gln Ser Ala Val Ser Thr Met Gln Gln Phe Tyr Gly
             80                  85                  90

atc cca gtc acc ggt gtg ttg gat cag aca aca atc gag tgg atg aag   398
Ile Pro Val Thr Gly Val Leu Asp Gln Thr Thr Ile Glu Trp Met Lys
         95                 100                 105

aaa cct cga tgt ggc gtc cct gat cat ccc cac ttg agc agg agg agg   446
Lys Pro Arg Cys Gly Val Pro Asp His Pro His Leu Ser Arg Arg Arg
    110                 115                 120

aga aat aag cga tat gcc cta act gga cag aag tgg agg cag aaa cac   494
Arg Asn Lys Arg Tyr Ala Leu Thr Gly Gln Lys Trp Arg Gln Lys His
125                 130                 135                 140

atc acc tac agc att cac aat tat acc cca aag gtg ggt gag ctg gac   542
Ile Thr Tyr Ser Ile His Asn Tyr Thr Pro Lys Val Gly Glu Leu Asp
                145                 150                 155

aca cgg aag gct att cgt cag gct ttc gat gtg tgg cag aag gtg act   590
Thr Arg Lys Ala Ile Arg Gln Ala Phe Asp Val Trp Gln Lys Val Thr
            160                 165                 170

cca ctg acc ttt gaa gag gtg cca tac cat gag atc aaa agt gac cgg   638
Pro Leu Thr Phe Glu Glu Val Pro Tyr His Glu Ile Lys Ser Asp Arg
        175                 180                 185

aag gag gca gac atc atg atc ttc ttt gct tct ggt ttc cat ggt gac   686
Lys Glu Ala Asp Ile Met Ile Phe Phe Ala Ser Gly Phe His Gly Asp
    190                 195                 200

agc tcc cca ttt gat ggg gaa ggg gga ttc cta gcc cat gcc tac ttt   734
Ser Ser Pro Phe Asp Gly Glu Gly Gly Phe Leu Ala His Ala Tyr Phe
205                 210                 215                 220

cct ggc cca ggg atc gga gga gac act cac ttt gat tca gat gaa ccc   782
Pro Gly Pro Gly Ile Gly Gly Asp Thr His Phe Asp Ser Asp Glu Pro
                225                 230                 235

tgg acg cta gga aat gcc aac cat gat ggc aat gac ctc ttc ctg gtg   830
Trp Thr Leu Gly Asn Ala Asn His Asp Gly Asn Asp Leu Phe Leu Val
            240                 245                 250
```

```
gcc gtg cat gaa ctg ggc cat gca ctg ggc ttg gag cac tct aat gac   878
Ala Val His Glu Leu Gly His Ala Leu Gly Leu Glu His Ser Asn Asp
        255                 260                 265

ccc agt gct atc atg gct ccc ttc tac caa tac atg gag aca cac aac   926
Pro Ser Ala Ile Met Ala Pro Phe Tyr Gln Tyr Met Glu Thr His Asn
    270                 275                 280

ttc aag cta ccg cag gac gat ctc cag ggc atc cag aag att tac gga   974
Phe Lys Leu Pro Gln Asp Asp Leu Gln Gly Ile Gln Lys Ile Tyr Gly
285                 290                 295                 300

ccc cca gct gag cct ctg gag ccc aca agg ccc ctc cat aca ctc ccg   1022
Pro Pro Ala Glu Pro Leu Glu Pro Thr Arg Pro Leu His Thr Leu Pro
                305                 310                 315

gtc cgc agg atc cac tcg ccg tct gag agg aag cac gag cgg cac cca   1070
Val Arg Arg Ile His Ser Pro Ser Glu Arg Lys His Glu Arg His Pro
            320                 325                 330

agg ccc cca cgg ccg ccc ctt ggg gac cgg cca tcc act cca ggt gcc   1118
Arg Pro Pro Arg Pro Pro Leu Gly Asp Arg Pro Ser Thr Pro Gly Ala
        335                 340                 345

aaa ccc aac atc tgc gat ggc aac ttc aac aca gtg gcc ctc ttc cga   1166
Lys Pro Asn Ile Cys Asp Gly Asn Phe Asn Thr Val Ala Leu Phe Arg
    350                 355                 360

ggg gag atg ttt gtg ttc aag gat cgc tgg ttc tgg cgc ctg cgc aat   1214
Gly Glu Met Phe Val Phe Lys Asp Arg Trp Phe Trp Arg Leu Arg Asn
365                 370                 375                 380

aac cgg gtg cag gaa ggc tac ccc atg cag atc gaa cag ttc tgg aag   1262
Asn Arg Val Gln Glu Gly Tyr Pro Met Gln Ile Glu Gln Phe Trp Lys
                385                 390                 395

ggc ctg ccc gcc cgc ata gac gca gcc tat gaa aga gct gac ggg aga   1310
Gly Leu Pro Ala Arg Ile Asp Ala Ala Tyr Glu Arg Ala Asp Gly Arg
            400                 405                 410

ttc gtc ttc ttc aaa gga gac aag tac tgg gtt ttc aaa gaa gtg acg   1358
Phe Val Phe Phe Lys Gly Asp Lys Tyr Trp Val Phe Lys Glu Val Thr
        415                 420                 425

gtg gaa cct ggg tac ccc cac agc ttg ggg gag ctg gga agc tgc ctg   1406
Val Glu Pro Gly Tyr Pro His Ser Leu Gly Glu Leu Gly Ser Cys Leu
    430                 435                 440

ccc cgt gaa gga att gac aca gct ctg cgc tgg gaa cct gtg ggc aaa   1454
Pro Arg Glu Gly Ile Asp Thr Ala Leu Arg Trp Glu Pro Val Gly Lys
445                 450                 455                 460
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acc tac ttc ttc aaa ggc gaa cgg tac tgg cgc tac agc gag gag cgg   1502
Thr Tyr Phe Phe Lys Gly Glu Arg Tyr Trp Arg Tyr Ser Glu Glu Arg
                465                 470                 475

cga gcc aca gac cct ggc tac ccc aag ccc atc acc gtg tgg aag ggc   1550
Arg Ala Thr Asp Pro Gly Tyr Pro Lys Pro Ile Thr Val Trp Lys Gly
            480                 485                 490

atc ccg cag gct ccg caa ggg gcc ttc atc agc aag gaa gga tat tac   1598
Ile Pro Gln Ala Pro Gln Gly Ala Phe Ile Ser Lys Glu Gly Tyr Tyr
        495                 500                 505

acc tac ttc tac aaa ggc cgg gac tac tgg aag ttt gac aac cag aaa   1646
Thr Tyr Phe Tyr Lys Gly Arg Asp Tyr Trp Lys Phe Asp Asn Gln Lys
    510                 515                 520

ctg agc gtg gag cca ggc tac cca cgc aac atc ctg cgt gac tgg atg   1694
Leu Ser Val Glu Pro Gly Tyr Pro Arg Asn Ile Leu Arg Asp Trp Met
525                 530                 535                 540

ggc tgc aag cag aag gag gta gag cgg cgt aag gag cgg agg ctg ccc   1742
Gly Cys Lys Gln Lys Glu Val Glu Arg Arg Lys Glu Arg Arg Leu Pro
                545                 550                 555

cag gat gat gtg gac atc atg gtg acc atc gat gac gtg cca ggc tct   1790
Gln Asp Asp Val Asp Ile Met Val Thr Ile Asp Asp Val Pro Gly Ser
            560                 565                 570

gtg aac gct gtg gct gtg gtt gtc ccc tgc aca ctg tcc ctc tgc ctc   1838
Val Asn Ala Val Ala Val Val Val Pro Cys Thr Leu Ser Leu Cys Leu
        575                 580                 585

ctg gtg ctg ctc tac act atc ttc caa ttc aag aac aag gcg ggt cct   1886
Leu Val Leu Leu Tyr Thr Ile Phe Gln Phe Lys Asn Lys Ala Gly Pro
    590                 595                 600

cag ccc gtc acc tac tat aag cgg ccg gtc cag gag tgg gta           1928
Gln Pro Val Thr Tyr Tyr Lys Arg Pro Val Gln Glu Trp Val
605                 610                 615

tgagcagccc agagccctct ctgtctaccc ggtctggcca gccaggccct tcctcaccag 1988

ggtctgaggg gcagctctag ccactgccca ctggggccag cagggctaag gcagggttcg 2048

tgtgtagctg aagtggtggg tgcactggtc taggctgagt gcggggctgg gagtgatggt 2108

ggctatgccc aggttgggta gctggcaccc agctgccagc cttctgtcct gggcagacct 2168

ctctctactc aagggaatag gccaggccct gtcaggagtc aaggatggtg ccaggaggtg 2228

cccctgaggt cattgcatcc tgtggtgtct gcaagatacc acagctccag tcctggctgg 2288
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gacccagccc tctgaggcaa gccagcacta gctctcaccc caccccaaga tgccaccaat 2348

cccagtcccc tctgccaaca cctgctggtc agatgtcccc tcatccctac cctactatcc 2408

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ctgtcatgtc gtgaatattt aaatgtcctg tcactactgt ttaaagtccc attttgcaaa 2648

ggctacttga ggctttaggt cagctagagg tgactgtctt ggtgatgagg ccagtatggt 2708

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agagcagtca gaggggcaaa gtactggagc ccccagagct cagcttcccc tcggcctggg 4148

tgacatcaca gcatctcagt gtcggtcaca ttttaaactg atcagccttt gtacaatgtt 4208

ttttaaatca tttctaaata aaacagaaat acagtgttaa aaaaaaaaaa aaaaa 4263

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<400> 8
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Met Pro Arg Ser Arg Gly Gly Arg Ala Ala Pro Gly Pro Pro Pro Pro
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ccg ccg ccg ccg ggc cag gcc ccg cgc tgg agc cgc tgg cgg gtc cct   96
Pro Pro Pro Pro Gly Gln Ala Pro Arg Trp Ser Arg Trp Arg Val Pro
            20                  25                  30

ggg cgg ctg ctg ctg ctg ctg ctg ccc gcg ctc tgc tgc ctc ccg ggc   144
Gly Arg Leu Leu Leu Leu Leu Leu Pro Ala Leu Cys Cys Leu Pro Gly
        35                  40                  45

gcc gcg cgg gcg gcg gcg gcg gcg gcg ggg gca ggg aac cgg gca gcg   192
Ala Ala Arg Ala Ala Ala Ala Ala Ala Gly Ala Gly Asn Arg Ala Ala
    50                  55                  60

gtg gcg gtg gcg gtg gcg cgg gcg gac gag gcg gag gcg ccc ttc gcc   240
Val Ala Val Ala Val Ala Arg Ala Asp Glu Ala Glu Ala Pro Phe Ala
65                  70                  75                  80

ggg cag aac tgg tta aag tcc tat ggc tat ctg ctt ccc tat gac tca   288
Gly Gln Asn Trp Leu Lys Ser Tyr Gly Tyr Leu Leu Pro Tyr Asp Ser
                85                  90                  95

cgg gca tct gcg ctg cac tca gcg aag gcc ttg cag tcg gca gtc tcc   336
Arg Ala Ser Ala Leu His Ser Ala Lys Ala Leu Gln Ser Ala Val Ser
            100                 105                 110
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act atg cag cag ttt tac ggg atc ccg gtc acc ggt gtg ttg gat cag 384
Thr Met Gln Gln Phe Tyr Gly Ile Pro Val Thr Gly Val Leu Asp Gln
115 120 125

aca acg atc gag tgg atg aag aaa ccc cga tgt ggt gtc cct gat cac 432
Thr Thr Ile Glu Trp Met Lys Lys Pro Arg Cys Gly Val Pro Asp His
130 135 140

ccc cac tta agc cgt agg cgg aga aac aag cgc tat gcc ctg act gga 480
Pro His Leu Ser Arg Arg Arg Arg Asn Lys Arg Tyr Ala Leu Thr Gly
145 150 155 160

cag aag tgg agg caa aaa cac atc acc tac agc att cac aac tat acc 528
Gln Lys Trp Arg Gln Lys His Ile Thr Tyr Ser Ile His Asn Tyr Thr
165 170 175

cca aaa gtg ggt gag cta gac acg cgg aaa gct att cgc cag gct ttc 576
Pro Lys Val Gly Glu Leu Asp Thr Arg Lys Ala Ile Arg Gln Ala Phe
180 185 190

gat gtg tgg cag aag gtg acc cca ctg acc ttt gaa gag gtg cca tac 624
Asp Val Trp Gln Lys Val Thr Pro Leu Thr Phe Glu Glu Val Pro Tyr
195 200 205

cat gag atc aaa agt gac cgg aag gag gca gac atc atg atc ttt ttt 672
His Glu Ile Lys Ser Asp Arg Lys Glu Ala Asp Ile Met Ile Phe Phe
210 215 220

gct tct ggt ttc cat ggc gac agc tcc cca ttt gat gga gaa ggg gga 720
Ala Ser Gly Phe His Gly Asp Ser Ser Pro Phe Asp Gly Glu Gly Gly
225 230 235 240

ttc ctg gcc cat gcc tac ttc cct ggc cca ggg att gga gga gac acc 768
Phe Leu Ala His Ala Tyr Phe Pro Gly Pro Gly Ile Gly Gly Asp Thr
245 250 255

cac ttt gac tcc gat gag cca tgg acg cta gga aac gcc aac cat gac 816
His Phe Asp Ser Asp Glu Pro Trp Thr Leu Gly Asn Ala Asn His Asp
260 265 270

ggg aac gac ctc ttc ctg gtg gct gtg cat gag ctg ggc cac gcg ctg 864
Gly Asn Asp Leu Phe Leu Val Ala Val His Glu Leu Gly His Ala Leu
275 280 285

gga ctg gag cac tcc agc gac ccc agc gcc atc atg gcg ccc ttc tac 912
Gly Leu Glu His Ser Ser Asp Pro Ser Ala Ile Met Ala Pro Phe Tyr
290 295 300

cag tac atg gag acg cac aac ttc aag ctg ccc cag gac gat ctc cag 960
Gln Tyr Met Glu Thr His Asn Phe Lys Leu Pro Gln Asp Asp Leu Gln
305 310 315 320

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ggc atc cag aag atc tat gga ccc cca gcc gag cct ctg gag ccc aca   1008
Gly Ile Gln Lys Ile Tyr Gly Pro Pro Ala Glu Pro Leu Glu Pro Thr
                325                 330                 335

agg cca ctc cct aca ctc ccc gtc cgc agg atc cac tca cca tcg gag   1056
Arg Pro Leu Pro Thr Leu Pro Val Arg Arg Ile His Ser Pro Ser Glu
            340                 345                 350

agg aaa cac gag cgc cag ccc agg ccc cct cgg ccg ccc ctc ggg gac   1104
Arg Lys His Glu Arg Gln Pro Arg Pro Pro Arg Pro Pro Leu Gly Asp
        355                 360                 365

cgg cca tcc aca cca ggc acc aaa ccc aac atc tgt gac ggc aac ttc   1152
Arg Pro Ser Thr Pro Gly Thr Lys Pro Asn Ile Cys Asp Gly Asn Phe
    370                 375                 380

aac aca gtg gcc ctc ttc cgg ggc gag atg ttt gtc ttt aag gat cgc   1200
Asn Thr Val Ala Leu Phe Arg Gly Glu Met Phe Val Phe Lys Asp Arg
385                 390                 395                 400

tgg ttc tgg cgt ctg cgc aat aac cga gtg cag gag ggc tac ccc atg   1248
Trp Phe Trp Arg Leu Arg Asn Asn Arg Val Gln Glu Gly Tyr Pro Met
                405                 410                 415

cag atc gag cag ttc tgg aag ggc ctg cct gcc cgc atc gac gca gcc   1296
Gln Ile Glu Gln Phe Trp Lys Gly Leu Pro Ala Arg Ile Asp Ala Ala
            420                 425                 430

tat gaa agg gcc gat ggg aga ttt gtc ttc ttc aaa ggt gac aag tat   1344
Tyr Glu Arg Ala Asp Gly Arg Phe Val Phe Phe Lys Gly Asp Lys Tyr
        435                 440                 445

tgg gtg ttt aag gag gtg acg gtg gag cct ggg tac ccc cac agc ctg   1392
Trp Val Phe Lys Glu Val Thr Val Glu Pro Gly Tyr Pro His Ser Leu
    450                 455                 460

ggg gag ctg ggc agc tgt ttg ccc cgt gaa ggc att gac aca gct ctg   1440
Gly Glu Leu Gly Ser Cys Leu Pro Arg Glu Gly Ile Asp Thr Ala Leu
465                 470                 475                 480

cgc tgg gaa cct gtg ggc aag acc tac ttt ttc aaa ggc gag cgg tac   1488
Arg Trp Glu Pro Val Gly Lys Thr Tyr Phe Phe Lys Gly Glu Arg Tyr
                485                 490                 495

tgg cgc tac agc gag gag cgg cgg gcc acg gac cct ggc tac cct aag   1536
Trp Arg Tyr Ser Glu Glu Arg Arg Ala Thr Asp Pro Gly Tyr Pro Lys
            500                 505                 510

ccc atc acc gtg tgg aag ggc atc cca cag gct ccc caa gga gcc ttc   1584
Pro Ile Thr Val Trp Lys Gly Ile Pro Gln Ala Pro Gln Gly Ala Phe
        515                 520                 525
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atc agc aag gaa gga tat tac acc tat ttc tac aag ggc cgg gac tac   1632
Ile Ser Lys Glu Gly Tyr Tyr Thr Tyr Phe Tyr Lys Gly Arg Asp Tyr
    530                 535                 540

tgg aag ttt gac aac cag aaa ctg agc gtg gag cca ggc tac ccg cgc   1680
Trp Lys Phe Asp Asn Gln Lys Leu Ser Val Glu Pro Gly Tyr Pro Arg
545                 550                 555                 560

aac atc ctg cgt gac tgg atg ggc tgc aac cag aag gag gtg gag cgg   1728
Asn Ile Leu Arg Asp Trp Met Gly Cys Asn Gln Lys Glu Val Glu Arg
                565                 570                 575

cgg aag gag cgg cgg ctg ccc cag gac gac gtg gac atc atg gtg acc   1776
Arg Lys Glu Arg Arg Leu Pro Gln Asp Asp Val Asp Ile Met Val Thr
            580                 585                 590

atc aac gat gtg ccg ggc tcc gtg aac gcc gtg gcc gtg gtc atc ccc   1824
Ile Asn Asp Val Pro Gly Ser Val Asn Ala Val Ala Val Val Ile Pro
        595                 600                 605

tgc atc ctg tcc ctc tgc atc ctg gtg ctg gtc tac acc atc ttc cag   1872
Cys Ile Leu Ser Leu Cys Ile Leu Val Leu Val Tyr Thr Ile Phe Gln
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Ile Asp Phe Ser Lys Ala Asp His Asn Asp Gly Tyr Pro Phe Asp Gly
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cct ggt ggc acg gtg gcc cac gca ttc ttc cct ggt gac cac cac acg   736
Pro Gly Gly Thr Val Ala His Ala Phe Phe Pro Gly Asp His His Thr
            205                 210                 215

gca ggg gac acc cac ttt gat gac gat gag cca tgg acc ttc cgt tcc   784
Ala Gly Asp Thr His Phe Asp Asp Asp Glu Pro Trp Thr Phe Arg Ser
        220                 225                 230

tca gat gcc cac ggg atg gac ctg ttt gca gtg gcc gtc cat gag ttt   832
Ser Asp Ala His Gly Met Asp Leu Phe Ala Val Ala Val His Glu Phe
    235                 240                 245

ggt cat gcc att ggt ctg agc cat gtt gcc gcc cca agc tcc atc atg   880
Gly His Ala Ile Gly Leu Ser His Val Ala Ala Pro Ser Ser Ile Met
250                 255                 260                 265

caa ccg tac tac cag ggc ccc gtg ggt gac ccc gta cgc tat gga ctt   928
Gln Pro Tyr Tyr Gln Gly Pro Val Gly Asp Pro Val Arg Tyr Gly Leu
                270                 275                 280

ccc tat gag gac agg gtg cgt gtc tgg cag ttg tac ggt gtg cgg gaa   976
Pro Tyr Glu Asp Arg Val Arg Val Trp Gln Leu Tyr Gly Val Arg Glu
            285                 290                 295

tcc gtg tcc cct act gcc cag ctg gat acc cca gag ccc gag gag cca   1024
Ser Val Ser Pro Thr Ala Gln Leu Asp Thr Pro Glu Pro Glu Glu Pro
        300                 305                 310

ccc ctc ctg cca gag ccc ccc aac aat cgg tct agc act ccg ccc cag   1072
Pro Leu Leu Pro Glu Pro Pro Asn Asn Arg Ser Ser Thr Pro Pro Gln
    315                 320                 325

aag gac gtg cct cac agg tgc act gcc cac ttt gat gct gtg gcc cag   1120
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```
Lys Asp Val Pro His Arg Cys Thr Ala His Phe Asp Ala Val Ala Gln
330                 335                 340                 345

att cga ggc gaa gca ttc ttt ttc aaa ggc aag tat ttc tgg agg ctg   1168
Ile Arg Gly Glu Ala Phe Phe Phe Lys Gly Lys Tyr Phe Trp Arg Leu
                350                 355                 360

acc cgg gac cga cac ttg gtg tcg ctg cag ccg gct caa atg cat cgc   1216
Thr Arg Asp Arg His Leu Val Ser Leu Gln Pro Ala Gln Met His Arg
            365                 370                 375

ttc tgg cgg ggc ctg ccg ctg cac ctg gac agt gtg gac gcc gtg tat   1264
Phe Trp Arg Gly Leu Pro Leu His Leu Asp Ser Val Asp Ala Val Tyr
        380                 385                 390

gag cgt acc agt gac cac aag att gtc ttc ttc aaa gga gac aga tac   1312
Glu Arg Thr Ser Asp His Lys Ile Val Phe Phe Lys Gly Asp Arg Tyr
    395                 400                 405

tgg gtg ttt aag gac aac aac gta gag gaa ggg tac ccg cga cct gtc   1360
Trp Val Phe Lys Asp Asn Asn Val Glu Glu Gly Tyr Pro Arg Pro Val
410                 415                 420                 425

tcc gac ttc agc ctc ccg cca ggt ggc atc gat gct gtc ttc tcc tgg   1408
Ser Asp Phe Ser Leu Pro Pro Gly Gly Ile Asp Ala Val Phe Ser Trp
                430                 435                 440

gcc cac aat gac agg act tat ttc ttt aag gac cag ctg tac tgg cgc   1456
Ala His Asn Asp Arg Thr Tyr Phe Phe Lys Asp Gln Leu Tyr Trp Arg
            445                 450                 455

tat gat gac cac aca cgg cgc atg gac cct ggc tac cct gcc cag gga   1504
Tyr Asp Asp His Thr Arg Arg Met Asp Pro Gly Tyr Pro Ala Gln Gly
        460                 465                 470

ccc ctg tgg aga ggt gtc ccc agc atg ttg gat gat gcc atg cgc tgg   1552
Pro Leu Trp Arg Gly Val Pro Ser Met Leu Asp Asp Ala Met Arg Trp
    475                 480                 485

tct gat ggt gca tcc tat ttc ttc cga ggc cag gag tac tgg aaa gtg   1600
Ser Asp Gly Ala Ser Tyr Phe Phe Arg Gly Gln Glu Tyr Trp Lys Val
490                 495                 500                 505

ctg gat ggc gag ctg gaa gca gcc ccc ggg tac cca cag tct aca gcc   1648
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Leu Asp Gly Glu Leu Glu Ala Ala Pro Gly Tyr Pro Gln Ser Thr Ala
                510                 515                 520

cgc gac tgg ctg gta tgc ggt gag ccg ctg gcg gat gcg gag gat gta   1696
Arg Asp Trp Leu Val Cys Gly Glu Pro Leu Ala Asp Ala Glu Asp Val
            525                 530                 535

ggg cct gga ccc cag ggc cgc agt ggg gcc caa gat ggt ctg gca gta   1744
Gly Pro Gly Pro Gln Gly Arg Ser Gly Ala Gln Asp Gly Leu Ala Val
        540                 545                 550

tgt tcc tgc act tca gac gca cac agg ttg gca ctg cca tct ctg ctg   1792
Cys Ser Cys Thr Ser Asp Ala His Arg Leu Ala Leu Pro Ser Leu Leu
    555                 560                 565

ctt ctg act cca ctg ctg tgg ggc ctg tgg acc tca gtc tct gcc aag   1840
Leu Leu Thr Pro Leu Leu Trp Gly Leu Trp Thr Ser Val Ser Ala Lys
570                 575                 580                 585

gca tcc tgagggcagt gctagccttg cggatcaagg agccagggga gcagggacac    1896
Ala Ser

actggccagt actcagcagg acttgtgctc caagcttccg gtccctcgct ccttccttcc 1956

ttccttcctt gaacccaggg gtgctgtgcc atctgctgga gtggtctcca gctgggacag 2016

gacgtcccac caagggcatc catgcacacc ttgcctacct ggagcagcca taggcagctc 2076

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accaggagca cagccacctc tccccgtcct agataggtta gccatggagg ctgtgtcctg 2496

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gctgcagaag ggcttctaac acctggaata aaggtgggcg ttcagtttag ggaaggagga 2736

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taatgagctc cagaaaggaa cagccaagtt caaaggttct gggacaagac gggcctgagg 2976

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caccctactc tgccctcata tcaaagcacg ctcctatgat gtcccatgtt gtccaccagc 3336

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cactgaaaac cagacccgca ggctggagct gtctagatgc tggtgtcaca ctcattttaa 3456

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cgggaccctg cacgccgccc gcgggcccat gtgagcgcc atg cgg cgc cgc gca    114
                                          Met Arg Arg Arg Ala
                                            1
                    5

gcc cgg gga ccc ggc ccg ccg ccc cca ggg ccc gga ctc tcg cgg ctg   162
Ala Arg Gly Pro Gly Pro Pro Pro Pro Gly Pro Gly Leu Ser Arg Leu
                  10                  15                  20

ccg ctg ctg ccg ctg ccg ctg ctg ctg ctg ctg gcg ctg ggg acc cgc   210
Pro Leu Leu Pro Leu Pro Leu Leu Leu Leu Leu Ala Leu Gly Thr Arg
              25                  30                  35

ggg ggc tgc gcc gcg ccg gaa ccc gcg cgg cgc gcc gag gac ctc agc   258
Gly Gly Cys Ala Ala Pro Glu Pro Ala Arg Arg Ala Glu Asp Leu Ser
          40                  45                  50

ctg gga gtg gag tgg cta agc agg ttc ggt tac ctg ccc ccg gct gac   306
Leu Gly Val Glu Trp Leu Ser Arg Phe Gly Tyr Leu Pro Pro Ala Asp
      55                  60                  65

ccc aca aca ggg cag ctg cag acg caa gag gag ctg tct aag gcc atc   354
Pro Thr Thr Gly Gln Leu Gln Thr Gln Glu Glu Leu Ser Lys Ala Ile
  70                  75                  80                  85

aca gcc atg cag cag ttt ggt ggc ctg gag gcc acc ggc atc ctg gac   402
Thr Ala Met Gln Gln Phe Gly Gly Leu Glu Ala Thr Gly Ile Leu Asp
                  90                  95                 100

gag gcc acc ctg gcc ctg atg aaa acc cca cgc tgc tcc ctg cca gac   450
Glu Ala Thr Leu Ala Leu Met Lys Thr Pro Arg Cys Ser Leu Pro Asp
              105                 110                 115

ctc cct gtc ctg acc cag gct cgc agg aga cgc cag gct cca gcc ccc   498
Leu Pro Val Leu Thr Gln Ala Arg Arg Arg Arg Gln Ala Pro Ala Pro
          120                 125                 130

acc aag tgg aac aag agg aac ctg tcg tgg agg gtc cgg acg ttc cca   546
Thr Lys Trp Asn Lys Arg Asn Leu Ser Trp Arg Val Arg Thr Phe Pro
      135                 140                 145

cgg gac tca cca ctg ggg cac gac acg gtg cgt gca ctc atg tac tac   594
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Arg Asp Ser Pro Leu Gly His Asp Thr Val Arg Ala Leu Met Tyr Tyr
150                 155                 160                 165

gcc ctc aag gtc tgg agc gac att gcg ccc ctg aac ttc cac gag gtg   642
Ala Leu Lys Val Trp Ser Asp Ile Ala Pro Leu Asn Phe His Glu Val
                170                 175                 180

gcg ggc agc acc gcc gac atc cag atc gac ttc tcc aag gcc gac cat   690
Ala Gly Ser Thr Ala Asp Ile Gln Ile Asp Phe Ser Lys Ala Asp His
            185                 190                 195

aac gac ggc tac ccc ttc gac ggc ccc ggc ggc acc gtg gcc cac gcc   738
Asn Asp Gly Tyr Pro Phe Asp Gly Pro Gly Gly Thr Val Ala His Ala
        200                 205                 210

ttc ttc ccc ggc cac cac cac acc gcc ggg gac acc cac ttt gac gat   786
Phe Phe Pro Gly His His His Thr Ala Gly Asp Thr His Phe Asp Asp
    215                 220                 225

gac gag gcc tgg acc ttc cgc tcc tcg gat gcc cac ggg atg gac ctg   834
Asp Glu Ala Trp Thr Phe Arg Ser Ser Asp Ala His Gly Met Asp Leu
230                 235                 240                 245

ttt gca gtg gct gtc cac gag ttt ggc cac gcc att ggg tta agc cat   882
Phe Ala Val Ala Val His Glu Phe Gly His Ala Ile Gly Leu Ser His
            250                 255                 260

gtg gcc gct gca cac tcc atc atg cgg ccg tac tac cag ggc ccg gtg   930
Val Ala Ala Ala His Ser Ile Met Arg Pro Tyr Tyr Gln Gly Pro Val
        265                 270                 275

ggt gac ccg ctg cgc tac ggg ctc ccc tac gag gac aag gtg cgc gtc   978
Gly Asp Pro Leu Arg Tyr Gly Leu Pro Tyr Glu Asp Lys Val Arg Val
    280                 285                 290

tgg cag ctg tac ggt gtg cgg gag tct gtg tct ccc acg gcg cag ccc   1026
Trp Gln Leu Tyr Gly Val Arg Glu Ser Val Ser Pro Thr Ala Gln Pro
295                 300                 305

gag gag cct ccc ctg ctg ccg gag ccc cca gac aac cgg tcc agc gcc   1074
Glu Glu Pro Pro Leu Leu Pro Glu Pro Pro Asp Asn Arg Ser Ser Ala
310                 315                 320                 325

ccg ccc agg aag gac gtg ccc cac aga tgc agc act cac ttt gac gcg   1122
```

```
Pro Pro Arg Lys Asp Val Pro His Arg Cys Ser Thr His Phe Asp Ala
                330                 335                 340

gtg gcc cag atc cgg ggt gaa gct ttc ttc ttc aaa ggc aag tac ttc   1170
Val Ala Gln Ile Arg Gly Glu Ala Phe Phe Phe Lys Gly Lys Tyr Phe
            345                 350                 355

tgg cgg ctg acg cgg gac cgg cac ctg gtg tcc ctg cag ccg gca cag   1218
Trp Arg Leu Thr Arg Asp Arg His Leu Val Ser Leu Gln Pro Ala Gln
        360                 365                 370

atg cac cgc ttc tgg cgg ggc ctg ccg ctg cac ctg gac agc gtg gac   1266
Met His Arg Phe Trp Arg Gly Leu Pro Leu His Leu Asp Ser Val Asp
    375                 380                 385

gcc gtg tac gag cgc acc agc gac cac aag atc gtc ttc ttt aaa gga   1314
Ala Val Tyr Glu Arg Thr Ser Asp His Lys Ile Val Phe Phe Lys Gly
390                 395                 400                 405

gac agg tac tgg gtg ttc aag gac aat aac gta gag gaa gga tac ccg   1362
Asp Arg Tyr Trp Val Phe Lys Asp Asn Asn Val Glu Glu Gly Tyr Pro
                410                 415                 420

cgc ccc gtc tcc gac ttc agc ctc ccg cct ggc ggc atc gac gct gcc   1410
Arg Pro Val Ser Asp Phe Ser Leu Pro Pro Gly Gly Ile Asp Ala Ala
            425                 430                 435

ttc tcc tgg gcc cac aat gac agg act tat ttc ttt aag gac cag ctg   1458
Phe Ser Trp Ala His Asn Asp Arg Thr Tyr Phe Phe Lys Asp Gln Leu
        440                 445                 450

tac tgg cgc tac gat gac cac acg agg cac atg gac ccc ggc tac ccc   1506
Tyr Trp Arg Tyr Asp Asp His Thr Arg His Met Asp Pro Gly Tyr Pro
    455                 460                 465

gcc cag agc ccc ctg tgg agg ggt gtc ccc agc acg ctg gac gac gcc   1554
Ala Gln Ser Pro Leu Trp Arg Gly Val Pro Ser Thr Leu Asp Asp Ala
470                 475                 480                 485

atg cgc tgg tcc gac ggt gcc tcc tac ttc ttc cgt ggc cag gag tac   1602
Met Arg Trp Ser Asp Gly Ala Ser Tyr Phe Phe Arg Gly Gln Glu Tyr
                490                 495                 500

tgg aaa gtg ctg gat ggc gag ctg gag gtg gca ccc ggg tac cca cag   1650
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Trp Lys Val Leu Asp Gly Glu Leu Glu Val Ala Pro Gly Tyr Pro Gln
                505                 510                 515

tcc acg gcc cgg gac tgg ctg gtg tgt gga gac tca cag gcc gat gga   1698
Ser Thr Ala Arg Asp Trp Leu Val Cys Gly Asp Ser Gln Ala Asp Gly
        520                 525                 530

tct gtg gct gcg ggc gtg gac gcg gca gag ggg ccc cgc gcc cct cca   1746
Ser Val Ala Ala Gly Val Asp Ala Ala Glu Gly Pro Arg Ala Pro Pro
    535                 540                 545

gga caa cat gac cag agc cgc tcg gag gac ggt tac gag gtc tgc tca   1794
Gly Gln His Asp Gln Ser Arg Ser Glu Asp Gly Tyr Glu Val Cys Ser
550                 555                 560                 565

tgc acc tct ggg gca tcc tct ccc ccg ggg gcc cca ggc cca ctg gtg   1842
Cys Thr Ser Gly Ala Ser Ser Pro Pro Gly Ala Pro Gly Pro Leu Val
                570                 575                 580

gct gcc acc atg ctg ctg ctg ctg ccg cca ctg tca cca ggc gcc ctg   1890
Ala Ala Thr Met Leu Leu Leu Leu Pro Pro Leu Ser Pro Gly Ala Leu
            585                 590                 595

tgg aca gcg gcc cag gcc ctg acg cta tgacacacag cgcgagccca         1937
Trp Thr Ala Ala Gln Ala Leu Thr Leu
        600                 605

tgagaggaca gaggcggtgg gacagcctgg ccacagaggg caaggactgt gccggagtcc 1997

ctgggggagg tgctggcgcg ggatgaggac gggccaccct ggcaccggaa ggccagcaga 2057

gggcacggcc cgccagggct gggcaggctc aggtggcaag gacggagctg tcccctagtg 2117

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            20                  25                  30

Leu Cys Cys Leu Ala Ala Ala Ala Gly Ala Gly Lys Pro Ala Gly Ala
        35                  40                  45

Asp Ala Pro Phe Ala Gly Gln Asn Trp Leu Lys Ser Tyr Gly Tyr Leu
    50                  55                  60

Leu Pro Tyr Glu Ser Arg Ala Ser Ala Leu His Ser Gly Lys Ala Leu
65                  70                  75                  80

Gln Ser Ala Val Ser Thr Met Gln Gln Phe Tyr Gly Ile Pro Val Thr
                85                  90                  95

Gly Val Leu Asp Gln Thr Thr Ile Glu Trp Met Lys Lys Pro Arg Cys
            100                 105                 110

Gly Val Pro Asp His Pro His Leu Ser Arg Arg Arg Arg Asn Lys Arg
        115                 120                 125

Tyr Ala Leu Thr Gly Gln Lys Trp Arg Gln Lys His Ile Thr Tyr Ser
    130                 135                 140

Ile His Asn Tyr Thr Pro Lys Val Gly Glu Leu Asp Thr Arg Lys Ala
145                 150                 155                 160

Ile Arg Gln Ala Phe Asp Val Trp Gln Lys Val Thr Pro Leu Thr Phe
                165                 170                 175

Glu Glu Val Pro Tyr His Glu Ile Lys Ser Asp Arg Lys Glu Ala Asp
            180                 185                 190

Ile Met Ile Phe Phe Ala Ser Gly Phe His Gly Asp Ser Ser Pro Phe
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195 200 205

Asp Gly Glu Gly Gly Phe Leu Ala His Ala Tyr Phe Pro Gly Pro Gly
210 215 220

Ile Gly Gly Asp Thr His Phe Asp Ser Asp Glu Pro Trp Thr Leu Gly
225 230 235 240

Asn Ala Asn His Asp Gly Asn Asp Leu Phe Leu Val Ala Val His Glu
245 250 255

Leu Gly His Ala Leu Gly Leu Glu His Ser Asn Asp Pro Ser Ala Ile
260 265 270

Met Ala Pro Phe Tyr Gln Tyr Met Glu Thr His Asn Phe Lys Leu Pro
275 280 285

Gln Asp Asp Leu Gln Gly Ile Gln Lys Ile Tyr Gly Pro Pro Ala Glu
290 295 300

Pro Leu Glu Pro Thr Arg Pro Leu His Thr Leu Pro Val Arg Arg Ile
305 310 315 320

His Ser Pro Ser Glu Arg Lys His Glu Arg His Pro Arg Pro Pro Arg
325 330 335

Pro Pro Leu Gly Asp Arg Pro Ser Thr Pro Gly Ala Lys Pro Asn Ile
340 345 350

Cys Asp Gly Asn Phe Asn Thr Val Ala Leu Phe Arg Gly Glu Met Phe
355 360 365

Val Phe Lys Asp Arg Trp Phe Trp Arg Leu Arg Asn Asn Arg Val Gln
370 375 380

Glu Gly Tyr Pro Met Gln Ile Glu Gln Phe Trp Lys Gly Leu Pro Ala
385 390 395 400

Arg Ile Asp Ala Ala Tyr Glu Arg Ala Asp Gly Arg Phe Val Phe Phe
405 410 415

Lys Gly Asp Lys Tyr Trp Val Phe Lys Glu Val Thr Val Glu Pro Gly
420 425 430

Tyr Pro His Ser Leu Gly Glu Leu Gly Ser Cys Leu Pro Arg Glu Gly
435 440 445

Ile Asp Thr Ala Leu Arg Trp Glu Pro Val Gly Lys Thr Tyr Phe Phe
450 455 460

Lys Gly Glu Arg Tyr Trp Arg Tyr Ser Glu Glu Arg Arg Ala Thr Asp
465 470 475 480

Pro Gly Tyr Pro Lys Pro Ile Thr Val Trp Lys Gly Ile Pro Gln Ala
485 490 495

Pro Gln Gly Ala Phe Ile Ser Lys Glu Gly Tyr Tyr Thr Tyr Phe Tyr
500 505 510

Lys Gly Arg Asp Tyr Trp Lys Phe Asp Asn Gln Lys Leu Ser Val Glu
515 520 525

Pro Gly Tyr Pro Arg Asn Ile Leu Arg Asp Trp Met Gly Cys Lys Gln
530 535 540

Lys Glu Val Glu Arg Arg Lys Glu Arg Arg Leu Pro Gln Asp Asp Val
545 550 555 560

Asp Ile Met Val Thr Ile Asp Asp Val Pro Gly Ser Val Asn Ala Val
565 570 575

Ala Val Val Val Pro Cys Thr Leu Ser Leu Cys Leu Leu Val Leu Leu
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Tyr Thr Ile Phe Gln Phe Lys Asn Lys Ala Gly Pro Gln Pro Val Thr
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Tyr Tyr Lys Arg Pro Val Gln Glu Trp Val
610 615

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35 40 45

Ala Ala Arg Ala Ala Ala Ala Ala Ala Gly Ala Gly Asn Arg Ala Ala
50 55 60

Val Ala Val Ala Val Ala Arg Ala Asp Glu Ala Glu Ala Pro Phe Ala
65 70 75 80

Gly Gln Asn Trp Leu Lys Ser Tyr Gly Tyr Leu Leu Pro Tyr Asp Ser
85 90 95

Arg Ala Ser Ala Leu His Ser Ala Lys Ala Leu Gln Ser Ala Val Ser
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Thr Met Gln Gln Phe Tyr Gly Ile Pro Val Thr Gly Val Leu Asp Gln
115 120 125

Thr Thr Ile Glu Trp Met Lys Lys Pro Arg Cys Gly Val Pro Asp His
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Pro His Leu Ser Arg Arg Arg Arg Asn Lys Arg Tyr Ala Leu Thr Gly
145 150 155 160

Gln Lys Trp Arg Gln Lys His Ile Thr Tyr Ser Ile His Asn Tyr Thr
165 170 175

Pro Lys Val Gly Glu Leu Asp Thr Arg Lys Ala Ile Arg Gln Ala Phe
180 185 190

Asp Val Trp Gln Lys Val Thr Pro Leu Thr Phe Glu Glu Val Pro Tyr
195 200 205

His Glu Ile Lys Ser Asp Arg Lys Glu Ala Asp Ile Met Ile Phe Phe
210 215 220

Ala Ser Gly Phe His Gly Asp Ser Ser Pro Phe Asp Gly Glu Gly Gly
225 230 235 240

Phe Leu Ala His Ala Tyr Phe Pro Gly Pro Gly Ile Gly Gly Asp Thr
245 250 255

His Phe Asp Ser Asp Glu Pro Trp Thr Leu Gly Asn Ala Asn His Asp
260 265 270

Gly Asn Asp Leu Phe Leu Val Ala Val His Glu Leu Gly His Ala Leu
275 280 285

Gly Leu Glu His Ser Ser Asp Pro Ser Ala Ile Met Ala Pro Phe Tyr
290 295 300

Gln Tyr Met Glu Thr His Asn Phe Lys Leu Pro Gln Asp Asp Leu Gln
305 310 315 320

Gly Ile Gln Lys Ile Tyr Gly Pro Pro Ala Glu Pro Leu Glu Pro Thr
325 330 335

Arg Pro Leu Pro Thr Leu Pro Val Arg Arg Ile His Ser Pro Ser Glu
340 345 350

Arg Lys His Glu Arg Gln Pro Arg Pro Pro Arg Pro Pro Leu Gly Asp
355 360 365

Arg Pro Ser Thr Pro Gly Thr Lys Pro Asn Ile Cys Asp Gly Asn Phe
370 375 380

Asn Thr Val Ala Leu Phe Arg Gly Glu Met Phe Val Phe Lys Asp Arg
385 390 395 400

Trp Phe Trp Arg Leu Arg Asn Asn Arg Val Gln Glu Gly Tyr Pro Met
405 410 415

Gln Ile Glu Gln Phe Trp Lys Gly Leu Pro Ala Arg Ile Asp Ala Ala
420 425 430

Tyr Glu Arg Ala Asp Gly Arg Phe Val Phe Phe Lys Gly Asp Lys Tyr
435 440 445

Trp Val Phe Lys Glu Val Thr Val Glu Pro Gly Tyr Pro His Ser Leu
450 455 460

Gly Glu Leu Gly Ser Cys Leu Pro Arg Glu Gly Ile Asp Thr Ala Leu
465 470 475 480

Arg Trp Glu Pro Val Gly Lys Thr Tyr Phe Phe Lys Gly Glu Arg Tyr
485 490 495

Trp Arg Tyr Ser Glu Glu Arg Arg Ala Thr Asp Pro Gly Tyr Pro Lys
500 505 510

Pro Ile Thr Val Trp Lys Gly Ile Pro Gln Ala Pro Gln Gly Ala Phe
515 520 525

Ile Ser Lys Glu Gly Tyr Tyr Thr Tyr Phe Tyr Lys Gly Arg Asp Tyr
530 535 540

Trp Lys Phe Asp Asn Gln Lys Leu Ser Val Glu Pro Gly Tyr Pro Arg
545 550 555 560

Asn Ile Leu Arg Asp Trp Met Gly Cys Asn Gln Lys Glu Val Glu Arg
565 570 575

Arg Lys Glu Arg Arg Leu Pro Gln Asp Asp Val Asp Ile Met Val Thr
580 585 590

Ile Asn Asp Val Pro Gly Ser Val Asn Ala Val Ala Val Val Ile Pro
595 600 605

Cys Ile Leu Ser Leu Cys Ile Leu Val Leu Val Tyr Thr Ile Phe Gln
610 615 620

Phe Lys Asn Lys Thr Gly Pro Gln Pro Val Thr Tyr Tyr Lys Arg Pro
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Val Gln Glu Trp Val
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Met Pro Arg Ser Arg Gly Gly Arg Ala Ala Pro Gly

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cag gcc tcg cgc tgg agc ggc tgg cgg gcc ccg ggg cgg ctg ctg ccg   158
Gln Ala Ser Arg Trp Ser Gly Trp Arg Ala Pro Gly Arg Leu Leu Pro
          15                  20                  25

ctg ctg ccc gcg ctc tgc tgc ctc gcg gcg gcg gcg ggg gcc ggg aag   206
Leu Leu Pro Ala Leu Cys Cys Leu Ala Ala Ala Ala Gly Ala Gly Lys
      30                  35                  40

ccg gcc ggg gcg gac gcg ccc ttc gct ggg cag aac tgg tta aaa tca   254
Pro Ala Gly Ala Asp Ala Pro Phe Ala Gly Gln Asn Trp Leu Lys Ser
 45                  50                  55                  60

tat ggc tat ctg ctt ccc tat gag tcg cgg gca tct gcg ttg cat tct   302
Tyr Gly Tyr Leu Leu Pro Tyr Glu Ser Arg Ala Ser Ala Leu His Ser
                    65                  70                  75

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Gly Lys Ala Leu Gln Ser Ala Val Ser Thr Met Gln Gln Phe Tyr Gly
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Ile Pro Val Thr Gly Val Leu Asp Gln Thr Thr Ile Glu Trp Met Lys
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Lys Pro Arg Cys Gly Val Pro Asp His Pro His Leu Ser Arg Arg Arg
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Arg Asn Lys Arg Tyr Ala Leu Thr Gly Gln Lys Trp Arg Gln Lys His
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Ile Thr Tyr Ser Ile His Asn Tyr Thr Pro Lys Val Gly Glu Leu Asp
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aca cgg aag gct att cgt cag gct ttc gat gtg tgg cag aag gtg act   590
Thr Arg Lys Ala Ile Arg Gln Ala Phe Asp Val Trp Gln Lys Val Thr
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cca ctg acc ttt gaa gag gtg cca tac cat gag atc aaa agt gac cgg   638
Pro Leu Thr Phe Glu Glu Val Pro Tyr His Glu Ile Lys Ser Asp Arg
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agc tcc cca ttt gat ggg gaa ggg gga ttc cta gcc cat gcc tac ttt   734
Ser Ser Pro Phe Asp Gly Glu Gly Gly Phe Leu Ala His Ala Tyr Phe
205                 210                 215                 220

cct ggc cca ggg atc gga gga gac act cac ttt gat tca gat gaa ccc   782
Pro Gly Pro Gly Ile Gly Gly Asp Thr His Phe Asp Ser Asp Glu Pro
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tgg acg cta gga aat gcc aac cat gat ggc aat gac ctc ttc ctg gtg   830
Trp Thr Leu Gly Asn Ala Asn His Asp Gly Asn Asp Leu Phe Leu Val
            240                 245                 250

gcc gtg cat gaa ctg ggc cat gca ctg ggc ttg gag cac tct aat gac   878
Ala Val His Glu Leu Gly His Ala Leu Gly Leu Glu His Ser Asn Asp
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ccc agt gct atc atg gct ccc ttc tac caa tac atg gag aca cac aac   926
Pro Ser Ala Ile Met Ala Pro Phe Tyr Gln Tyr Met Glu Thr His Asn
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Phe Lys Leu Pro Gln Asp Asp Leu Gln Gly Ile Gln Lys Ile Tyr Gly
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Pro Pro Ala Glu Pro Leu Glu Pro Thr Arg Pro Leu His Thr Leu Pro
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Val Arg Arg Ile His Ser Pro Ser Glu Arg Lys His Glu Arg His Pro
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agg ccc cca cgg ccg ccc ctt ggg gac cgg cca tcc act cca ggt gcc   1118
Arg Pro Pro Arg Pro Pro Leu Gly Asp Arg Pro Ser Thr Pro Gly Ala
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Asn Arg Val Gln Glu Gly Tyr Pro Met Gln Ile Glu Gln Phe Trp Lys
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Gly Leu Pro Ala Arg Ile Asp Ala Ala Tyr Glu Arg Ala Asp Gly Arg
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Phe Val Phe Phe Lys Gly Asp Lys Tyr Trp Val Phe Lys Glu Val Thr
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gtg gaa cct ggg tac ccc cac agc ttg ggg gag ctg gga agc tgc ctg   1406
Val Glu Pro Gly Tyr Pro His Ser Leu Gly Glu Leu Gly Ser Cys Leu
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Pro Arg Glu Gly Ile Asp Thr Ala Leu Arg Trp Glu Pro Val Gly Lys
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acc tac ttc ttc aaa ggc gaa cgg tac tgg cgc tac agc gag gag cgg   1502
Thr Tyr Phe Phe Lys Gly Glu Arg Tyr Trp Arg Tyr Ser Glu Glu Arg
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Arg Ala Thr Asp Pro Gly Tyr Pro Lys Pro Ile Thr Val Trp Lys Gly
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Ile Pro Gln Ala Pro Gln Gly Ala Phe Ile Ser Lys Glu Gly Tyr Tyr
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acc tac ttc tac aaa ggc cgg gac tac tgg aag ttt gac aac cag aaa   1646
Thr Tyr Phe Tyr Lys Gly Arg Asp Tyr Trp Lys Phe Asp Asn Gln Lys
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Leu Ser Val Glu Pro Gly Tyr Pro Arg Asn Ile Leu Arg Asp Trp Met
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cag gat gat gtg gac atc atg gtg acc atc gat gac gtg cca ggc tct   1790
Gln Asp Asp Val Asp Ile Met Val Thr Ile Asp Asp Val Pro Gly Ser
            560                 565                 570

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Val Asn Ala Val Ala Val Val Val Pro Cys Thr Leu Ser Leu Cys Leu
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ctg gtg ctg ctc tac act atc ttc caa ttc aag aac aag gcg ggt cct   1886
Leu Val Leu Leu Tyr Thr Ile Phe Gln Phe Lys Asn Lys Ala Gly Pro
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Gln Pro Val Thr Tyr Tyr Lys Arg Pro Val Gln Glu Trp Val
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Pro Pro Pro Pro Gly Gln Ala Pro Arg Trp Ser Arg Trp Arg Val Pro
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Gly Arg Leu Leu Leu Leu Leu Leu Pro Ala Leu Cys Cys Leu Pro Gly
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Ala Ala Arg Ala Ala Ala Ala Ala Ala Gly Ala Gly Asn Arg Ala Ala
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Val Ala Val Ala Val Ala Arg Ala Asp Glu Ala Glu Ala Pro Phe Ala
65 70 75 80

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Gly Gln Asn Trp Leu Lys Ser Tyr Gly Tyr Leu Leu Pro Tyr Asp Ser

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Arg Ala Ser Ala Leu His Ser Ala Lys Ala Leu Gln Ser Ala Val Ser
            100                 105                 110

act atg cag cag ttt tac ggg atc ccg gtc acc ggt gtg ttg gat cag   384
Thr Met Gln Gln Phe Tyr Gly Ile Pro Val Thr Gly Val Leu Asp Gln
        115                 120                 125

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Thr Thr Ile Glu Trp Met Lys Lys Pro Arg Cys Gly Val Pro Asp His
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Pro His Leu Ser Arg Arg Arg Arg Asn Lys Arg Tyr Ala Leu Thr Gly
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Gln Lys Trp Arg Gln Lys His Ile Thr Tyr Ser Ile His Asn Tyr Thr
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cca aaa gtg ggt gag cta gac acg cgg aaa gct att cgc cag gct ttc   576
Pro Lys Val Gly Glu Leu Asp Thr Arg Lys Ala Ile Arg Gln Ala Phe
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Asp Val Trp Gln Lys Val Thr Pro Leu Thr Phe Glu Glu Val Pro Tyr
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cat gag atc aaa agt gac cgg aag gag gca gac atc atg atc ttt ttt   672
His Glu Ile Lys Ser Asp Arg Lys Glu Ala Asp Ile Met Ile Phe Phe
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gct tct ggt ttc cat ggc gac agc tcc cca ttt gat gga gaa ggg gga   720
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Phe Leu Ala His Ala Tyr Phe Pro Gly Pro Gly Ile Gly Gly Asp Thr
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gga ctg gag cac tcc agc gac ccc agc gcc atc atg gcg ccc ttc tac   912
Gly Leu Glu His Ser Ser Asp Pro Ser Ala Ile Met Ala Pro Phe Tyr
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Gln Tyr Met Glu Thr His Asn Phe Lys Leu Pro Gln Asp Asp Leu Gln
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ggc atc cag aag atc tat gga ccc cca gcc gag cct ctg gag ccc aca  1008
Gly Ile Gln Lys Ile Tyr Gly Pro Pro Ala Glu Pro Leu Glu Pro Thr
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Arg Pro Leu Pro Thr Leu Pro Val Arg Arg Ile His Ser Pro Ser Glu
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Arg Lys His Glu Arg Gln Pro Arg Pro Pro Arg Pro Pro Leu Gly Asp
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cgg cca tcc aca cca ggc acc aaa ccc aac atc tgt gac ggc aac ttc  1152
Arg Pro Ser Thr Pro Gly Thr Lys Pro Asn Ile Cys Asp Gly Asn Phe
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Asn Thr Val Ala Leu Phe Arg Gly Glu Met Phe Val Phe Lys Asp Arg
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Trp Phe Trp Arg Leu Arg Asn Asn Arg Val Gln Glu Gly Tyr Pro Met
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cag atc gag cag ttc tgg aag ggc ctg cct gcc cgc atc gac gca gcc  1296
Gln Ile Glu Gln Phe Trp Lys Gly Leu Pro Ala Arg Ile Asp Ala Ala
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Arg Lys Glu Arg Arg Leu Pro Gln Asp Asp Val Asp Ile Met Val Thr
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Ile Asn Asp Val Pro Gly Ser Val Asn Ala Val Ala Val Val Ile Pro
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